

ANNALS of SURGERY

A MONTHLY REVIEW OF SURGICAL SCIENCE AND PRACTICE

Also the Official Publication of the American
Surgical Association, the Southern Surgical
Association, Philadelphia Academy of
Surgery, and New York Surgical Society

VOLUME 112

JULY—DECEMBER

1940

J B LIPPINCOTT COMPANY, Publishers

PHILADELPHIA

MONTREAL

LONDON

NEW YORK

COPYRIGHT 1940
J B LIPPINCOTT COMPANY

MADE IN THE UNITED STATES OF AMERICA

CONTRIBUTORS TO VOLUME 112

	Page
ABELL, IRVIN, Louisville, Ky	1035
ABELL, JR., IRVIN, Louisville, Ky	1035
ABBOTT, W. OSLER, Philadelphia Pa	584
ANDRUS, WILLIAM DEWITT, New York N Y	783
ARNHEIM, ERNEST E., New York N Y	352
ARONSON, SHEPARD GERARD Brooklyn, N Y	400
BAKER, CHARLES P. Omaha Neb	1006
BATSON OSCAR V. Philadelphia, Pa	138
BEIL, H. GLENN, San Francisco Calif	763
BELIAS JOSEPH E., Peoria Ill	112
BERGLER, R. A., Richmond Va	22
BIGGER, I. A., Richmond, Va	879
BISGARD J. DEWITT Omaha Neb	1006
BLAIR, VIRRAY P. St Louis Mo	287
BLALOCK ALFRED, Nashville Tenn	557
BOYS FLOYD, Charlottesville Va	969
BRASELTON, JR. C. W. Galveston, Texas	212
BROOKS BARNEY, Nashville, Tenn	130
BRUCKEN, A. J. Pittsburgh Pa	378
BULL DAVID C., New York, N Y	498
BYARS LOUIS T., St Louis, Mo	287
CAVE, HENRY W., New York, N Y	747
CAYLOR, HAROLD D., Bluffton, Ind	310
COLCOCK BENTLEY P., Boston, Mass	671
COLEY, BRADLEY L., New York, N Y	1114
COLLER FREDERICK A., Ann Arbor, Mich	256, 520
DARRACH, WILLIAM, New York, N Y	795
DAVIS, LINCOLN, Boston, Mass	318
DAVIS, LOYAL, Chicago, Ill	1058
DE YOE, LEON E., Paterson, N J	127
DREW, CHARLES R. New York, N Y	498
DUNCAN, GEORGE W., Nashville, Tenn	130
EGGERS, CARL, New York, N Y	315
EHLER, ADRIAN A., Albany, N Y	426
EHRENTHEIL, OTTO, Boston, Mass	1042
ELKIN, DANIEL C., Atlanta, Ga	280, 895
ELKINGTON, J. RUSSELL, Philadelphia, Pa	150, 158
ELMAN, ROBERT, St Louis, Mo	234, 594
ELOESSER LEO, San Francisco, Calif	1067

	Page
FERGUSON, L KRAEER, Philadelphia, Pa	454
FINE, JACOB, Boston, Mass	240, 546
FORSTER, ARMAND C, St Louis, Mo	370
FRANCONA, NICHOLAS T, Chicago, Ill	225
FRANTZ, V KNEELAND, New York, N Y	161
FREEMAN, NORMAN E, Philadelphia, Pa	960
GAGE, MIMS, New Orleans, La	938, 975
GAMBLE, JAMES L, Boston, Mass	314
GENDEL, SAMUEL, Los Angeles, Calif	240
GLENN, FRANK, New York, N Y	64
GRANET, EMIL New York, N Y	440
GREEN, WARREN W, Toledo, Ohio	297
GREENLEE, D P, Pittsburgh, Pa	378
GROPER, MORRIS J, San Francisco, Calif	344
GROSS, ROBERT E, Boston, Mass	51
HARE, HUGH F, Boston, Mass	977
HARKEN, DWIGHT E, New York, N Y	I
HARTMAN, FRANK W, Detroit, Mich	791
HAY, LYLE, Minneapolis, Minn	626
HEINBECKER, PETER, St Louis, Mo	1101
HOLMAN, CRANSTON W New York, N Y	339
HOLMAN, EMILE, San Francisco Calif	840
HORINE, CYRUS F, Baltimore, Md	471
HORSLEY, GUY W, Richmond, Va	22
HOUSER, MILES S, Bluffton, Ind	360
HURLEY, ANSON G, Muncie, Ind	392
HURWITZ, ALFRED, Boston, Mass	546
IRVIN, J LOGAN, Detroit, Mich	530
IVY, ROBERT H, Philadelphia, Pa	775
JACKSON, REGINALD H, Madison, Wis	219
KAY, EARLE B, Ann Arbor, Mich	700
KEARNS, JR, J E, Evanston, Ill	421
KIRSHBAUM, JACK D, Chicago, Ill	225
LADD, WILLIAM E, Boston, Mass	51
LAHEY, FRANK H, Boston, Mass	671, 977
LEE, WALTER ESTELLE, Philadelphia, Pa	150, 311, 313, 960, 1134, 1135
LEHMAN, EDWIN P, Charlottesville, Va	969
LEMMON, WILLIAM T, Philadelphia, Pa	31
LINDER, HAROLD H, San Francisco, Calif	321
LLOYD, J G, Pittsburgh, Pa	378
LORD, JR, JERE W, New York, N Y	783
LOWER, WILLIAM E, Cleveland, Ohio	100

	Page
MACFILL, WILLIAM F, New York, N Y	1071
MADDOCK WALTER G Ann Arbor, Mich	520
MAGATH THOMAS B, Rochester, Minn	271
MARINO A W MARTIN, Brooklyn, N Y	417
MARK JLROME Boston Mass	546
MARTIN JOHN, Chicago, Ill	1058
MATAS RUDOLPH New Orleans, La	802, 909
McCLURE ROY D, Detroit, Mich	791
McELROY, W S, Pittsburgh, Pa	378
McLAUGHLIN, EDWARD F, Philadelphia, Pa	122
MEYER, HLBERT WILLY, New York N Y	37
MINOT A S Nashville, Tenn	557
MOORE R M, Galveston, Texas	212
MOORE WILL C Muncie Ind	392
MORRIS JOHN H New York, N Y	I
NAFFZIGER, HOWARD C, San Francisco Calif	763
NERP, LOUIS, Brooklyn N Y	417
NEUHOF, HAROLD New York, N Y	291
NICHOLSON, JESSE T Philadelphia Pa	305
NICKEL JR WILLIAM F New York N Y	747
OCHSNER ALTON, New Orleans, La	938
PARRAN, THOMAS, Washington, D C	480
PASCHAL, JR GEORGE W, Philadelphia, Pa	31
PEARSE HERMAN E, Rochester, N Y	923
PENBLRTHY GROVER C Detroit, Mich	530
PLIERS JOHN P, New Haven Conn	490
PLTEPSON, EDWARD W, New York, N Y	80
POOL, JOHN L, New York, N Y	1114
RANSOM HENRY K, Ann Arbor, Mich	700
RAVDIN, I S, Philadelphia, Pa	576
RIA, CHARLES E, Minneapolis, Minn	300
RHOADS, JONATHAN E, Philadelphia, Pa	158, 568
ROBERTSON, DAVID E, Toronto, Canada	687
ROTHENBERG, ROBERT E, Brooklyn, N Y	400
ROYSTER, HUBERT A, Raleigh, N C	1129
SAMSON, PAUL C, Oakland, Calif	201
SAMUELS, SAUL S, New York, N Y	105
SANDUSKY, WILLIAM R, New York, N Y	339
SAUNDERS, JOHN B deC, San Francisco, Calif	321
SCUDDER, JOHN, New York, N Y	502
SHIH, H E, Peiping, China	249
SHUMACKER, JR, HARRIS B, Baltimore, Md	177
SMITHWICK, REGINALD H, Boston, Mass	1085

	Page
SOMMER, JR, GEORGE N J, Tinton, N J	426
SPARROW, THOMAS D, Charlotte, N C	87
STOUT, ARTHUR PURDY, New York, N Y	284
SULLIVAN, RALPH C, Chicago, Ill	225
TENERY, R MAYO, Detroit, Mich	530
THOMPSON, WESLEY D, Philadelphia, Pa	454
TRACH, BENEDICT, Minneapolis, Minn	626
TURRELL, ROBERT, Brooklyn, N Y	417
VALK, WILLIAM L, Ann Arbor, Mich	256
VAN DUYN, E S, Syracuse, N Y	294
VAN DUYN, 2nd, JOHN, Syracuse, N Y	294
VARCO, RICHARD L, Minneapolis, Minn	626
VERLOT, MAX G, Boston, Mass	1042
WALPOLE, STEWART, Minneapolis, Minn	626
WALTER, CARL W, Boston, Mass	603
WALTERS, WALTMAN, Rochester, Minn	271
WANG, SHAO-HSUN, Peiping, China	249
WANGENSTEEN, OWEN H, Minneapolis, Minn	626
WARREN, SHIELDS, Boston, Mass	977
WHIPPLE, ALLEN O, New York, N Y	481
WHITE, JAMES C, Boston, Mass	1042
WHITE, WILLIAM CRAWFORD, New York, N Y	769
WILLARD, DEFOREST P, Philadelphia, Pa	305
WISE, WALTER D, Baltimore, Md	798
WOLFF, WILLIAM A, Philadelphia, Pa	150 158

ANNALS OF SURGERY

VOL 112

JULY, 1940

No 1



THE SUPERIOR PULMONARY SULCUS "TUMOR OF PANCOAST" IN RELATION TO HARE'S SYNDROME

JOHN H. MORRIS, M.D., AND DWIGHT E. HARKEN, M.D.

NEW YORK, N. Y.

FROM THE LABORATORIES OF PATHOLOGY AND THE FOURTH SURGICAL DIVISION, BUFFALO HOSPITAL,
NEW YORK, N. Y.

UNDER the term of "Superior Pulmonary Sulcus Tumor," Pancoast,¹ in 1932 redescrbed a group of intrathoracic neoplasms presenting certain distinctive features which appeared to differentiate them from the tumors commonly occurring in this region and which in his opinion, justified their isolation and classification as a "new" pathologic entity. According to this author, these tumors were identified (1) Physically, by a precise, constant localization in the superior thoracic inlet adjacent to the pulmonary apex, a histologic picture of epidermoid carcinoma, and a site of origin demonstrably independent of the neighboring lung, pleura, ribs, vertebrae, mediastinum, or of metastatic foci. (2) Clinically, by an aggregation of clinical manifestations, the essential components of which are (a) Horner's syndrome—expressing involvement of the cervical sympathetic. (b) Pain referred to shoulder, arm and hand, associated with muscular atrophy—indicative of invasion of the brachial plexus. (c) Roentgenologic evidence of a small homogeneous apical shadow together with destructive infiltration of contiguous ribs and vertebrae. Emphasizing their epithelial structure and conceding that the exact site of origin remains uncertain, Pancoast nevertheless indulged in the hypothesis that these tumors have their inception in bronchial epithelial rests, pointing out, in support of this theory, the constant localization of the tumor in a region where bronchial rests are prone to persist, the absence of any other demonstrable primary focus, and, finally, a histologic picture of squamous cell epithelioma which is compatible with a bronchial origin.

The formation of new clinical entities has long been a popular method of approach to clinical problems in general, and, regardless of the intrinsic merit of these new classifications, the method itself has served an important purpose in the sense that it constitutes a challenge to the established order and, as such, tends to bring out a profitable controversial response directed at the problem under consideration. Pancoast's publication proved to be no exception to this principle, for the "Superior Pulmonary Sulcus Tumor" speedily became the center of a spirited controversy which displayed a tendency to question

the justification for the isolation of this tumor as a new entity, as well as to discredit the specificity of the clinical syndrome ascribed to it. In the light of this discussion, it is apparent that opposition to the Pancoast hypothesis is based primarily on three types of evidence: (1) That the clinical syndrome described as a specific manifestation of the "Superior Pulmonary Sulcus Tumor" may be, and frequently is, induced by a variety of neoplastic, traumatic, inflammatory and metastatic lesions arising near the pulmonary apex; (2) That the entity is founded upon assumptions which are unjustifiable in view of the inadequate evidence, gross and microscopic, submitted by its author; (3) That in no reported case has scientific proof of branchial origin of these tumors been presented.

For example, Tobias² studied five cases in which apical tumors were associated with the essential features of the syndrome in question, and was able to prove that four were primary carcinomata of the lung, while the fifth was a metastatic tumor from carcinoma of the stomach. Browder and DeVeer³ reported five cases presenting apical tumors plus the typical clinical manifestations described by Pancoast, and demonstrated by postmortem studies that of these, three were primary carcinomata of the lung, one was metastatic from a hypernephroma, while the last proved to be a tumor of the thymus. Evans⁴ observed five clinically typical cases, in each of which a different variety of apical tumor was found. In a case reported by Frost and Wolpaw⁵ the characteristic clinical features of the "Superior Pulmonary Sulcus Tumor" were noted in conjunction with a sympathicoblastoma arising from the inferior cervical ganglion. Fried⁶ encountered an instance of primary carcinoma of the left apex in which chest pain and Horner's syndrome were induced by metastases to the cervicodorsal spine and ribs, and points out that a similar origin has not been ruled out in Pancoast's cases. Seigent⁷ showed that Horner's syndrome occasionally occurs in advanced apical tuberculosis, due to extension of inflammatory tissue to the oculosympathetic pathway.

From these and other observations, the fact has been established that the symptom complex described by Pancoast may be initiated by a wide variety of lesions arising in the vicinity of the pulmonary apex, *viz.*, primary tumors of the lung, largely bronchogenic carcinoma, tumors arising from tissues adjacent to the pulmonary apex from pleura, periosteum, bone, mediastinum, miscellaneous conditions such as apical tuberculosis, aneurysms and trauma, and finally, metastatic tumors from numerous distant primary foci. This fact has tended to enhance the skepticism relative to the integrity of the "Superior Pulmonary Sulcus Tumor" as an entity, and majority opinion has been determined thereby. At the same time there is a disposition on the part of a minority of observers to recognize the existence of an apical tumor possessing certain characteristics which set it apart from the tumors commonly occurring in this region. Steiner and Francis,⁸ for instance, report three such cases, in which the location and clinical manifestations are identical with those of the "Superior Pulmonary Sulcus Tumor" and, according to these authors, "the clinical findings and gross pathologic characteristics are quite unlike the picture expected in carcinoma of the lung." Nevertheless, it

appears from the necropsy record in two of the cases that these tumors had a definite pulmonary origin, that they were identified histologically as adenocarcinomata, and that they disclosed no morphologic evidence pointing to a bronchial relationship. Furthermore, Jacox⁹ presented a case exhibiting similar clinical and postmortem findings, and this writer comments that these tumors "fulfill all the criteria of the entity previously described as 'Pulmonary Sulcus Tumor'." The clinical features of this condition represent a definite and striking syndrome quite different from that of the usual primary malignant growths of the lung. Both the latter observers coincide in the conclusion that these tumors "are a clinically distinct and unrecognized type of cancer" and that "the 'Superior Pulmonary Sulcus Tumor' is an atypical form of bronchogenic carcinoma."

These records may be taken as typical of the general sentiment relative to the Pancoast entity and, in evaluating their significance, the conclusion is inescapable that certain deductions based upon them are untenable. In the first place, it is apparent from analysis of the case records quoted above, that in each instance, the apical pathologic changes in question were either frankly primary lung tumors in which secondary extension accounted for the clinical manifestations, or that these symptoms were induced by pathologic changes, neoplastic or otherwise, whose histologic and morphologic features traced their origin definitely to known tissues adjacent to the apical region, *e g*, sarcoma, epithelioma, metastatic carcinoma, aneurysm, *etc*. Since the "Pancoast tumor," among other features, is distinguished by its "lack of origin from lung, pleura, ribs or mediastinum," the above noted instances obviously fail to qualify and evidence based upon them cannot be pertinent to the present discussion. Furthermore, since the tumor described by Jacox⁹ is definitely a lung tumor, it cannot, on these grounds, "fulfill all the criteria of the entity previously described as pulmonary sulcus tumor," despite the fact that it does "represent a definite and striking syndrome quite different from that of the usual primary malignant growth of lung."

In the second place, reference has been made to a group of cases which established the fact that the clinical syndrome described as a specific manifestation of the "Superior Pulmonary Sulcus Tumor" may also be induced by a variety of pathologic lesions occurring in the vicinity of the pulmonary apex, and this fact, in the opinion of many writers, destroys the integrity of this entity. It must be recognized, however, that this syndrome represents merely one element of the entity itself, that it is only an expression of pressure destruction effects upon bone and nerve tissues in the apical region, and that it accordingly varies in degree depending upon the character and extent of the lesion. The absence of this symptom complex in the clinical picture does not preclude the existence of a true "Pancoast tumor" and, likewise, neither does its presence in association with other tumors impair its significance as an element in the entity known as the "Superior Pulmonary Sulcus Tumor."

As regards the bronchial origin of the "Superior Pulmonary Sulcus Tumor," it must be conceded that such a relationship is difficult to substantiate

by direct testimony. As pointed out by Geschickter and Denison,¹⁰ tracing the source of these tumors, purely on the basis of the histologic structure, often leads to erroneous conclusions. They classify carcinomata of the lung into two groups, of which the common hilar or epidermoid type arises from the basal cell layer beneath the lining cells of the large bronchi, later involving the pleura to produce a picture simulating the "Pancoast tumor." Referring to neoplasms arising from bronchial epithelium, Carp and Stout¹¹ stress the fact that although the absence of a discoverable primary focus plus distinctive gross and histologic features are strong presumptive evidence of an origin from bronchial cleft epithelium, in no reported case has scientific proof of such origin been presented. Nevertheless, Symmers,¹² under whose direction the pathologic material constituting the present report was assembled, is authority for the statement that, in some instances, the "Pancoast tumor" may exhibit histologic evidence of its bronchial origin, and the authors propose to submit, at a later point, case records with histologic material to support this assertion.

Terplan¹³ states that malignant epithelial tumors of the Pancoast variety may originate from either lung or pleura, in the former instance, a primary carcinoma of the lung is said to grow into the pleural cavity and spread along the pleural surface mushroom-fashion, while in the latter case, tumors primary in the pleura may differentiate into an epithelial type suggestive of the Pancoast picture, in both instances, it is to be inferred, these tumors may be readily confused with the "Superior Pulmonary Sulcus Tumor." On the other hand, McFarland¹⁴ contends that lung tumors of this cell type are not apt to be found in an apical lung lesion so far from the larger bronchi, and he further believes it to be highly improbable that a tumor of the lung with such meager lung involvement could be primary to such an extensive extra-pleural invasion. However this may be, it is at least apparent that biopsy only is not competent to establish the identity of the "Superior Pulmonary Sulcus Tumor," and that the final verdict must rest upon complete post-mortem studies which are adequate not only to exclude these local imitators but to demonstrate, as well, the nonexistence of any sources of metastatic deposits.

In the main, the assumption of a bronchial origin for the "Superior Pulmonary Sulcus Tumor" must necessarily be founded upon evidence which, although of an indirect type, is nevertheless impressive. Given a malignant epithelial tumor, primary in the apical region where no epithelial tissue is found normally and granted the opportunity to exclude the lung, pleura and other local structures as a source, this assumption is not unwarranted. The lateral walls of the primitive pharynx present five bronchial arches with four successively intervening grooves lined externally by ectoderm and internally by entoderm. These grooves, especially the second, occasionally present perforations of the floor which persist as bronchial fistulae on the side of the neck, and it is well recognized that these persistent epithelial remnants are particularly prone to initiate epithelial neoplasms. Caudal to the fifth pharyngeal arch there may appear an evanescent fifth groove the posterior

wall of which may show a transient condensation of mesenchyme suggesting a sixth arch, the so-called ultimobranchial groove and body. These embryonal tissues contribute no definite adult structures and their ultimate fate is not known. Pancoast suggests that persistent epithelial rests from these or others of the lower branchial clefts may serve as points of departure for the primary epithelial neoplasms of this region. According to Wenglow ski¹⁵ branchial anomalies can occur only above the hyoid bone and the thymopharyngeal duct is the anlage for cysts and fistulae below this point. He points out that the thymus is an entodermal evagination from the ventral part of the third groove and that it communicates with the pharynx by means of the thymopharyngeal duct. This duct passes caudally and laterally, subsequently reaching the suprasternal area in the substance of the thymus. The upper portion of the duct obliterates but its distal portion persists as an epithelial-lined tract which is suggested as a source of cysts and fistulae in this region.

It is our impression, on reviewing the foregoing discussion, that much of the evidence thus far submitted in opposition to the Pancoast hypothesis may legitimately be impeached on the grounds that it fails to give due consideration to the scope and definition of the entity as originally described. According to our interpretation, this entity is built around the concept of a specific malignant apical neoplasm which is identified histologically by the picture of epidermoid carcinoma and grossly by its 'lack of origin from lung, pleura, ribs or mediastinum'. If this be true, it follows that tumors of the apical region whose gross and morphologic features indicate an origin from any of the above noted structures do not "fulfill the criteria of the entity previously described as Superior Pulmonary Sulcus Tumor" regardless of the fact that they may produce identical clinical and roentgenologic manifestations. It should again be emphasized, in this connection, that these manifestations noted as essential elements of the Pancoast syndrome, represent after all merely the effects of pressure-destruction on adjacent nerve trunks, and it is, therefore, obvious that any of the varied types of apical tumors capable of exerting such pressure-destruction may be expressed symptomatically in a similar manner. For example, it is well recognized that adenocarcinoma of the pulmonary apex may induce Horner's syndrome, arm pain and roentgenographic evidence of apical tumor, but this fact does not establish a connection between adenocarcinoma of the lung and the "Superior Pulmonary Sulcus Tumor" as some writers seem to suggest. In short, the qualifications for the entity under consideration resolve themselves into two essential, complementary criteria: (1) A primary epithelial neoplasm, specific in location, morphology and environment—the "Superior Pulmonary Sulcus Tumor", and (2) a group of nonspecific clinical and roentgenologic manifestations which are incidental to the mechanical presence of the tumor—the so-called Pancoast syndrome.

Briefly stated, therefore, the point at issue in this controversy is whether there exists at the superior thoracic inlet a tumor which fulfills the criteria set forth for the "Superior Pulmonary Sulcus Tumor," and this question awaits answer. The negative side of the argument has succeeded merely in

demonstrating the nonspecificity of the syndrome itself, but for reasons previously noted, this fact does not invalidate the original hypothesis. On the other hand, the affirmative side is, likewise, open to criticism for its failure to establish the existence of this tumor. For example, Pancoast, upon whom the burden of proof obviously rests, presented, in support of his theory, seven cases exhibiting a characteristic clinical picture, but the evidential value of this series is impaired by the fact that it provided only two biopsies and no necropsies. In the meantime, however, this deficiency has been compensated for by contributions from other sources.

In 1934, Clarke¹⁶ observed a patient who presented an apical shadow with erosion of ribs and vertebral bodies, associated with typical arm pain, muscular atrophy and Horner's syndrome. At necropsy, the tumor, which proved to be an epithelioma, was found to be extrapleural although adherent to the lung, and Clarke, finding it difficult to conceive of a bronchogenic source, gave consideration to its origin from an embryonal rest.

In 1935, Fried¹⁷ reported the autopsy findings in two cases of apical tumor which had exhibited, clinically, every aspect of Pancoast's syndrome. In each instance, the tumor mass, although completely filling the apical region of the thorax and compressing the upper lobe from above downwards, was separated from the lung by pleura and could be detached therefrom without loss of substance. Histologically, these tumors were epitheliomata, and as careful search failed to disclose a pleural or pulmonary origin, and since they both arose in areas where epithelial tissue is not normally present, it was assumed that they originated in epithelial rests embedded in the region of the sternoclavicular articulation. Fried concludes that although the clinical syndrome is not pathognomonic, the tumor itself represents a well-defined entity for which he proposed the name sternoclavicular branchioma. Gjaef and Steinberg,¹⁸ in 1936, studied, during life and at necropsy in this laboratory, a classic case of apical tumor exhibiting the Pancoast syndrome, and particularly emphasized the fact that the tumor was attached only by adhesions to the lung, and that the spread of the tumor cells on the pleura was limited to a thin plaque. Microscopic study of this tumor disclosed a malignant epithelial neoplasm exhibiting the usual squamous epithelial arrangement with occasional evidences in some areas of a glandular pattern, and this picture, they point out, is not incompatible with branchial origin.

These instances establish the fact that there does exist at the superior thoracic inlet a malignant epithelial neoplasm, intimately associated with the lung but demonstrably extrapleural in location, and capable of inducing the clinical syndrome described by Pancoast. To add the final touch required to complete the picture of the "Superior Pulmonary Sulcus Tumor," it only remains to verify the primary nature of the tumor *in situ* by excluding the possibility of foci elsewhere in the body. McCarthy¹⁹ states that he has seen several intrathoracic tumors with primary focus in the nasopharynx, and it is obvious that the routine autopsy cannot be relied upon to settle the problem under consideration. It is evident, therefore, that the criteria determining the selection and identification of the "Superior Pulmonary Sulcus Tumor"

must be based, not only upon clinical and roentgenographic data, but must include as well, biopsy, study, operative exposure of the tumor and, finally, the opportunity to carry out a complete, meticulous postmortem study inclusive of every structure in the body

It is the primary purpose of the present report to record our observations based upon the study of a series of apical chest tumors which, in view of the character of the preceding discussion, contribute important data thereto and in our opinion, adequately establish the "Superior Pulmonary Sulcus Tumor" as a *specific entity*. This series comprises eight cases, all of which exhibit the classic picture of Horner's syndrome associated with the typical apical shadow, characteristic pain distribution and muscular atrophy. In three of these cases, the apical tumor was shown to be either bronchogenic or metastatic carcinoma and thus served to illustrate the *nonspecific nature of the syndrome* itself, two cases, which were undoubtedly true Pancoast tumors, were, nevertheless, disqualified because of incomplete pathologic studies, there remain, therefore, three instances which "fulfill all the criteria of the entity previously described as primary 'Pulmonary Sulcus Tumor'". These criteria, which, according to our conception, determine the selection of these tumors, may be summarized as follows

(1) Clinical evidence of an apical tumor expressed in terms of pressure-destruction effects upon adjacent nerve and osseous tissues—(Hare's syndrome)

(2) Histologic evidence of epithelioma

(3) Pathologic evidence, based upon biopsy, operative and postmortem studies, which are competent to prove (a) the extrapulmonary character of the tumor, (b) its "lack of origin from lung, pleura, ribs or mediastinum", and (c) its primary nature as determined by especially planned methods designed to exclude all possible sources of metastatic origin

If this standard is applied to the selection of "Superior Pulmonary Sulcus Tumors," there appear but four instances in the literature, one reported by Clarke, in 1934, two by Fried, in 1935, and one by Graef and Steinberg, in 1936, which conform satisfactorily, and thus, since three of our own cases seem to be acceptable on this basis, a total number of only seven authentic cases have been recorded to date

In presenting our own material, it seems expedient for purposes of analysis, to do so under three headings

I Cases typifying the nonspecific nature of Pancoast's syndrome (Hare's syndrome) together with brief discussion of the history and clinical aspects of this condition

II Consideration of three cases of apical tumor, which are presented as instances of true "Superior Pulmonary Sulcus Tumors"

III Analysis of the clinical symptoms of the "Superior Pulmonary Sulcus Tumor"

I *Hare's Syndrome*—The syndrome, about which this discussion has centered, presenting (a) Horner's syndrome—expressing involvement of the

cervical sympathetic chain, (b) pain referred to shoulder, arm and hand, ~~associated with muscular atrophy indicative of invasion of the brachial~~ plexus, and (c) an apical tumor with destructive infiltration of contiguous ribs and vertebrae—popularly recognized as Pancoast's syndrome

It has, however, been pointed out by Fulton,²⁰ in his article on Horner's syndrome, and again by Browder and DeVee,³ that the syndrome was fully described a century ago by Edward Selleck Hare,²¹ then House Surgeon to the Stafford County General Infirmary in England. His name, however, like that of many other observers who lived when medicine was an art, is lost to the eponymic nomenclature of to-day. On the contrary so many names are falsely glorified, as in the instance of "Horner's syndrome" itself, as illustrated not only in Hare's report but in a clinic and pathologic report from the files of Bellevue Hospital, in 1868.

Hare reviewed the ocular signs and symptoms in the presence of destruction of the lowest cervical sympathetic ganglion, 31 years later to be identified with the name of Horner. Hare went even further and described all of the components of the still broader syndrome, including irritation of the brachial plexus, which has recently been identified with the name of Pancoast.

Hare's patient was a male, age 40, who presented himself complaining of pain, tingling and numbness in left arm along course of the ulnar nerve. There was a small tumor situated in the "inferior triangular space." Hare attributed the pain to brachial plexus involvement and observed that "the pupil of the left eye became contracted and the levator palpebrae ceased to perform its office." Treatment with opiates, mercurials, leeches, blisters and belladonna, was futile and the man died. Necropsy revealed "A tumor possessing the hardness of scirrhous extending under the sternocleidomastoideus and trapezius and was seen to extend upwards as far as the origin of the brachial plexus. The carotid artery, internal jugular vein and pneumogastric nerve passed into its substance, the first remaining pervious, the two last were lost and transformed into the diseased structure, as were also the phrenic nerve and farther down the sympathetic, with its lowest cervical ganglion. The tumor lay upon the third and fourth nerves of the plexus, both of which were inseparable from it." This represents but a part of the detailed description of the tumor and its relations. Except for the fact that microscopic examination of tissues was not an accessible aid in 1838, Hare's case is as complete as any now available.

In 1859, MacDonnell stressed the significance of myosis as a sign of intra-thoracic tumors. Colby²² responded by calling attention to his report of 1850, in which a female, age 17, suffered from pain in the shoulder and "shooting pains down the arm and into the fingers." A small tumor was palpable above the left clavicle and there was ptosis of the left eyelid with constriction of the pupil. Although necropsy was performed, the detailed findings were not described. Subsequently a large number of cases of intra-thoracic disease causing myosis, were reported. Most of these were by French writers and were ascribed to tuberculosis.

Klumpke,²³ in 1885, commenting on arm paralyses and brachial plexus injury, mentioned the, not uncommon, ocular changes in the form of the Claude Bernard-Horner syndrome. She reported two cases with arm pain, anesthesia, paralysis, ptosis and myosis. The brachial plexus and sympathetic injuries were on a traumatic basis.

Several instances have been cited in which the syndrome was caused by aneurysms. The description of such an aneurysm is to be found in the records of Bellevue Hospital for the year 1868, one year before Horner defined his syndrome and its etiology. The Bellevue case presented a subclavian aneurysm which caused pain that radiated down the right arm and ptosis of the eyelid on the same side was noted. Valentine Mott ligated the innominate and carotid arteries. The patient lived 24 days after operation. Necropsy revealed erosion of the first three ribs and vertebrae on the right side. Death was caused by rupture of an aneurysm of the innominate artery some distance below the point of ligation. Another case, similar in almost every detail, was reported in 1886, by May.²⁴ This patient was placed on a "Tufnell's aneurysm diet," but became clamorous for food and unwilling to continue the restricted diet, so that it was necessary to resort to the hunterian operation. The patient died from hemorrhage on the eighteenth day after operation. Necropsy demonstrated erosion of the upper ribs posteriorly as well as erosion of the first dorsal vertebra.

While the precise definition of the Hare syndrome necessitates a neoplastic etiology, it has been pointed out that tuberculosis, osteoarthritis, and trauma have brought about a similar clinical picture. More to the point is it significant, that it has been possible to glean from medical literature a total of 48 cases in which the Hare syndrome has had an actual neoplastic origin. Obviously, these show striking clinical and roentgenologic uniformity, but due to the paucity of adequate pathologic study, it is possible to make a sound presumptive diagnosis in only 30 reports. These include 20, probable bronchogenic, carcinomata, two definite osteogenic sarcomata, one from a vertebra and the other from a rib, one definite sympathicoblastoma, two metastatic carcinomata, one from the stomach, the other from a breast, one metastatic tumor, probably from a hypernephroma, and, finally, one "carcinoma of the thymus."

Those instances in which the Hare syndrome has arisen as a result of apparently primary "Superior Pulmonary Sulcus Tumors" have already received consideration.

With an appreciation for the pathologic nonspecificity, yet clinical unity of the components of this syndrome, and in view of the excellent clinical and physiopathologic discussion of Edward Sellick Hare, 100 years ago, it seems most appropriate to designate this syndrome as the "Hare syndrome."

In view of the large number of cases that have been reported in the literature, illustrating varied neoplastic derivation of Hare's syndrome, it suffices to review briefly three of the six cases that have been observed in Bellevue Hospital.

Case 1—Hare's Syndrome Chart No 45, Path No 11754 F E, white, male, age 48, was admitted to the Fourth Division of Bellevue Hospital, complaining of constant boring pain in the left shoulder which radiated down the arm into the hand. This pain had increased steadily over a period of eight months and had been almost unbearable during the previous three weeks. During this period there had been a conspicuous tendency toward swelling of this extremity. There had been a weight loss of 33 pounds, most of which had occurred during the preceding three months. There were no other symptoms directing attention to intrathoracic disease.

Physical Examination revealed an emaciated man with considerable edema of the left arm. Both pupils were contracted, but there was a marked ptosis of the left eyelid. Examination of the chest disclosed a smooth, firm mass filling the left supraclavicular fossa and infraclavicular fulness on the same side. The corresponding region was found to be flat to percussion and devoid of breath sounds on auscultation down to the level of the fourth rib. The only other noteworthy finding was a firm mass in the left lobe of the prostate, which was estimated at 3x3x3 cm.

Roentgenologic examination revealed a circumscribed mass filling the region of the left pulmonic field, above the level of the fifth rib. Destructive changes were noted in the first and second ribs posteriorly.

Notwithstanding roentgenotherapy, the patient grew steadily weaker over a period of two months. During the third month in the hospital and terminal month of life, urinary retention necessitated repeated catheterization. He died in uremic coma on the fifty-eighth day of hospitalization.

Necropsy revealed a primary alveolar carcinoma of the left lobe of the prostate with multiple metastases to the lungs. There were also metastases in the first two ribs on the left side, with infiltration of the surrounding soft tissues and cervical extension as far upward and medially as the thyroid gland. The brachial plexus and cervical sympathetic chain on the left side were incorporated in the metastatic carcinomatous mass.

COMMENT—This patient was originally thought to be suffering from primary bronchogenic carcinoma in which the Hare syndrome was the only conspicuous clinical feature. It was not until the last month of life that the primary carcinoma of the prostate produced direct symptoms.

Case 2—Hare's Syndrome P O'C, white, male, age 49, was admitted to Bellevue Hospital complaining of pain in the right axilla and scapular region. This pain had first been noticed one and one-half years before admission but it had become more severe and constant during the preceding three weeks. There were no dyspnea, cough, hemoptysis, night sweats or other symptoms directing attention to any intrathoracic disease.

Physical Examination revealed a well-developed and well-nourished man. There was enophthalmus of the left eye, contraction of the pupil and marked ptosis of the corresponding eyelid. On examination of the chest, marked tenderness to pressure was noted anteriorly down to the third rib and posteriorly to the level of the spinous process of the fifth dorsal vertebra. On percussion posteriorly, there was flatness at the right apex shading into dullness down to the angle of the scapula. Over the corresponding area and in the supraclavicular fossa, distant breath sounds were heard.

Fluoroscopic examination revealed a dense nodular shadow which extended from the right hilus, obliquely upward, and completely filled the right pulmonic field immediately above and below the clavicle. These findings were confirmed roentgenologically.

The seven millimeter bronchoscope was passed and the mucous membrane of the right bronchus was observed to be thickly coated with mucus and to have lost its normal color. The upper portion of the right upper lobe was fixed in position so that its bronchus could not be brought into view. There was no evidence of neoplastic growth into the lumina of the bronchi.

In spite of roentgenotherapy, the patient led a rapidly downward course to death in two months

Necropsy revealed primary adenocarcinoma of the right main bronchus extending up over the apex of the lung extrapleurally, without lung involvement. There was erosion of the first and second ribs on the right side, the clavicle, the sixth and seventh cervical and the first and second dorsal vertebral bodies. The brachial plexus and cervical sympathetic chain were extensively involved in the tumor mass. Metastatic nodules were found in the liver, in both kidneys and in both adrenal glands.

COMMENT—This case constitutes an example of Hare's syndrome, derived from infiltration of the structures in the region of the thoracic inlet by an adenocarcinoma of bronchogenic origin.

Case 3—*Hare's Syndrome*. E. S., white, male, age 47, was admitted to the Fourth Division of Bellevue Hospital, complaining of pain in the right shoulder, which had been first felt nine months previously, and was intermittent in character. For the past six months the pain had been constant. The patient also complained that he had been slowly "losing his voice." A weight loss of 60 pounds had been noticed since the onset of symptoms.

Physical Examination revealed a well-developed and well-nourished, florid man, with slight fulness of the right side of his face. There was marked congestion of the veins of the neck on the right side and on the anterior aspect of the chest down to the diaphragmatic line.

A partial Horner's syndrome of the right eye was manifested by ptosis of the eyelid and contraction of the pupil which measured two millimeters in diameter, although the pupil of the left eye measured five millimeters in diameter. There was no definite enophthalmos.

On examination of the chest, a soft mass filled the right supraclavicular fossa. The right apex was dull to percussion as far down as the angle of the scapula posteriorly and to the second intercostal space anteriorly. Breath sounds over the area of dullness were distant and bronchial in character.

Over the distribution of the right ulnar nerve there was marked diminution of tactile sensation. Clubbing of the fingernails was present in the right hand but not in the left.

Roentgenologic examination revealed a circumscribed mass occupying the upper half of the right pulmonic field. After a course of roentgenotherapy to the upper half of the right side of the thorax, the patient's symptoms improved sufficiently that he insisted upon being discharged to the Out-Patient Department. He failed to continue his roentgenotherapy and has been lost to the Follow-Up Clinic, so that his subsequent course remains in doubt.

COMMENT—This case presents two clinical features not uncommon concomitants of Hare's syndrome, namely, venous obstruction at the thoracic inlet and involvement of the recurrent laryngeal nerve. It further emphasizes the uncertainty in differentiating primary "Pulmonary Sulcus Tumors" from other neoplasms without pathologic study.

II *Presentation of Cases*—This group comprises three instances of apical tumor whose clinical and roentgenologic manifestations suggested a primary diagnosis of "Superior Pulmonary Sulcus Tumor" and this diagnosis appears to be adequately substantiated by the character of the gross and histologic data submitted.



FIG 1—Apical tumor Case 1 Showing rib erosion



FIG 2—Bronchogram Case 1 Showing intact bronchial tree and posterosuperior compression of upper lobe



FIG 3—Bronchogram, Case 1 Lateral aspect showing posterosuperior position and relationships of tumor mass

Case 1—Chart No 60050, Path No 2838136 C S, white, male, age 47, was admitted to the Fourth Surgical Division Bellevue Hospital, June 6, 1936, complaining of severe, stabbing pain referred to the right shoulder and radiating down the right arm. At the onset of this pain, five months previously, and because of the attendant rapid loss of weight and appetite, the patient had been admitted to another hospital where, after two months observation, a diagnosis of pulmonary tuberculosis was made and artificial pneumothorax instituted. Subsequent to discharge, the pain became more severe and the patient became so weak and dyspneic that he applied for admission to



FIG 4—Gross specimen Case 1 Pleural surface

another hospital where examination disclosed a slightly tender mass between the border of the scapula and the vertebral column on the right side. Roentgenograms at this time revealed, in addition to the pneumothorax at the right base, a rounded, homogeneous shadow at the right apex and in the infraclavicular region. The third to the sixth ribs posteriorly showed evidence of destruction and a tentative diagnosis of osteogenic sarcoma was made. At this time repeated sputum examinations were negative for tuberculosis but the Wassermann reaction was strongly positive.

Upon admission to Bellevue Hospital the patient appeared emaciated, dyspneic and cyanotic. The pain, which had become exceedingly severe, radiated from the shoulder region into the axilla and across the right scapular region to be eventually referred down the arm, particularly into the fourth and fifth fingers. In addition he complained of a constant, dry, nonproductive cough, shortness of breath, anorexia, and a progressive weight loss of 25 pounds over the preceding four months' period.

Physical Examination was essentially negative except for the local condition. Temperature averaged 100° F rectally, and pulse 100 to 120. Blood count showed 3,500,000 red cells with 65 per cent hemoglobin. Horner's syndrome was not present, neurologic examination gave negative results, and there was no evidence of venous dilatation over chest or neck.

Over the right interscapular region a firm, solid, tender swelling bulged through the intercostal spaces rising four centimeters above the surface and measuring nine centimeters in diameter at the base. This area was flat to percussion and there was com-



FIG 5—Gross specimen, Case 1. Tumor sectioned to show character of cut section.

plete absence of breath sounds over the apical region anteriorly and posteriorly, while posteriorly, below, a pleural rub and moist rales could be heard. Roentgenograms disclosed a dense, circumscribed mass occupying the right upper hemithorax with erosion of the third to sixth ribs posteriorly and thickening of axillary pleura from apex to base (Fig 1). A bronchogram, after injection by Doctor Stanford, of the right upper lobe bronchus, showed an intact bronchial tree but indicated that this lobe was compressed from above and behind (Fig 2). Simultaneous lateral and stereoscopic studies disclosed the posterosuperior position and relationships of the tumor mass (Fig 3).

At this time, a specimen of the tumor, obtained by aspiration biopsy (Doctor Higginbotham) was submitted to Doctor Symmers and Doctor Hutcheson, both of whom concurred in the tentative histologic diagnosis of epidermoid carcinoma.

Under observation, the symptoms became progressively worse and the pain intractable so that considering the hopeless prognosis without intervention, it was decided

to attempt a palliative surgical removal of the tumor. A preoperative diagnosis of Pancoast tumor was made and, under cyclopropane intratracheal anesthesia, the thorax was approached through a right posterior scapular incision. The scapula was turned laterally to permit the section of the second to fifth ribs well to the outer side of the tumor as well as close to their angles, and thus a bloc removal of the tumor with the involved rib segments was attempted. The tumor was then seen to completely surround the first to the sixth ribs, extending into the neck and invading both lower cervical and upper dorsal vertebral bodies (Figs 4 and 5). Anteriorly, the tumor compressed the right upper lobe but was definitely extrapleural, the visceral pleura stripping readily away from the tumor mass without loss of substance. The tumor was, therefore, completely mobilized except in its posterosuperior portion where its dense attachment in the angle between ribs and corresponding vertebral bodies rendered complete removal impossible.



FIG 6—Photomicrograph of Tumor in Case 1. Showing (a) sheets of hyperchromatic polyhedral epithelial cells poorly differentiated, (b) areas of 'prickle' cells, (c) whorls of squamous cells with epithelial pearls.



FIG 7—Photomicrograph of Squamous Cell Epithelioma in Case 2. Showing abundant, dense fibrous stroma regarded as characteristic of a bronchogenic origin.

The postoperative course was stormy, with the development during the first 24 hours of considerable serosanguineous fluid in right chest which necessitated thoracentesis. During the second postoperative day contralateral pulmonary edema further complicated the picture and death followed from cardiocirculatory failure on the second postoperative day.

At autopsy, remnants of the tumor were found infiltrating the planes between the scalenus muscles, the brachial plexus was widely invaded, and the cervical sympathetic chain was lost in the tumor tissue. The routine autopsy was supplemented by a careful search designed to rule out the existence of primary or metastatic tumor foci and included complete investigation of the head, sinuses, pharynx, adrenals, lungs, bronchial trees, etc. Since these efforts produced negative results, it was felt that the primary character of the apical tumor was quite effectively established.

Microscopic sections (Fig 6) revealed sheets of hyperchromatic, polyhedral epithelial cells showing very little differentiation. In some areas, cytoplasmic bridges or "prickle cells" were noted, while in others squamous cell whorls with epithelial "pearls" were observed. A histologic diagnosis of epithelioma of unknown origin was made by Doctor Symmers.

Additional sections, to include the visceral pleura and subjacent lung in proximity to the tumor, adequately establish the fact that the neoplastic process is abruptly limited by the former and that no invasion of the latter has taken place despite the extensive infiltration of neighboring ribs, vertebrae, etc.

COMMENT—In summary, therefore, Case 1 presents a primary, extrapleural, squamous cell epithelioma arising in the posteriosuperior thoracic gutter and exhibiting a tendency toward destructive infiltration of adjacent ribs, vertebrae and nerve trunks. The extrapleural character of this tumor appears to be adequately established by the gross and microscopic evidence submitted and a bronchial or pulmonary origin can be effectively ruled out. At the same time, its classification as primary *in situ* may be predicated upon the results of special studies designed to exclude all other possible sources of origin. It is worthy of note, in view of the marked involvement of the cervical sympathetic trunk as demonstrated by autopsy, that Horner's syndrome was conspicuously absent, thus indicating that this sign is not necessarily pathognomonic of apical tumors. Finally, the relative immunity of the lung to neoplastic invasion is of interest in the face of the extensive involvement of the neighboring ribs, vertebrae and muscle planes.

Case 2—Path No 19278 A J, Negro, age 47, was admitted to the hospital complaining of pain originating in the right scapular region and radiating to the right shoulder axilla and upper arm. The pain, which was first noted four months previous to admission, had recently assumed an agonizing character and was associated with dyspnea, general weakness and a weight loss of 40 pounds since onset of illness.

Physical Examination revealed a moderately emaciated patient who presented a soft mass bulging the supra- and infraclavicular fossae on the right side. There was marked atrophy of the shoulder muscles and percussion disclosed an area of flatness posteriorly down to the level of the third dorsal spine and anteriorly as low as the second rib. The right pupil was much smaller than the left, the corresponding palpebral fissure was distinctly narrowed and there was a definite degree of enophthalmos present.

Roentgenologic examination demonstrated a dense homogeneous mass occupying the right apical region, and there was evidence of extensive destruction of the first with partial erosion of the second rib posteriorly. In addition, a large cavity was observed at the right apex.

Operation, undertaken three weeks after admission, disclosed an extensive, inoperable tumor of the apex and operative procedure was limited to the removal of material for biopsy.

The patient died on the sixth postoperative day, and a complete autopsy was carried out. The tumor occupied the posteriosuperior portion of the thoracic inlet and was densely adherent in the region of the first and second ribs and their corresponding vertebrae, all of which were eroded. The right apex of the lung was compressed and adherent to the tumor mass but could be easily separated therefrom and showed no gross evidence of infiltration thereby. Careful search of the lung and bronchial tree disclosed no evidence of neoplastic tissue, and it was felt that these structures could not have given origin to the tumor, although investigation failed to reveal any neoplastic foci in other parts of the body.

Dr Douglas Symmers, under whose direction this work was later undertaken, reviewed these sections (Fig 7) without knowledge of the autopsy findings and pointed out that the dense and abundant fibrous stroma of this squamous cell epithelioma is characteristic of the epitheliomata of branchiogenic origin. He felt justified in making a diagnosis of squamous cell epithelioma of branchiogenic origin, in this instance on a his-

tologic basis alone. This opinion was in accord with the autopsy findings, though arrived at independently.

COMMENT—Case 2 presents an extrapleural, apical tumor which proved to be an epidermoid carcinoma. Horner's syndrome, referred arm and shoulder pain, and erosion of ribs and vertebrae completed the clinical picture. Complete postmortem studies failed to disclose foci elsewhere in the body. The postmortem diagnosis was "Superior Pulmonary Sulcus Tumor." This case is unique in that a presumptive gross diagnosis of primary "Pulmonary Sulcus Tumor" was made by exclusion at necropsy, and independently confirmed by histologic studies.

Case 3—Path No. 24819. G. I., white, male, age 42, was admitted to Bellevue Hospital, August 16, 1937. Seven months previously he had first experienced a sharp, intermittent pain in the right arm and shoulder. Two months later this pain had become very severe, and was at this time also referred to the right axilla, scapular and infra-clavicular regions. For the past five months he had complained of a chronic cough which had recently become productive of a thick, tenacious, yellow sputum, but at no time had blood been noted. During the past several weeks he had developed a progressive weakness and anorexia, and stated that he had lost 35 pounds during the last five-month period. Throughout this interval he said he had felt "feverish" each afternoon but had not observed any associated night sweats. He had been a chronic alcoholic for several years but denied venereal infection or disease.

Physical Examination—The patient appeared emaciated, pallid and acutely ill. The right pupil was smaller than the left but there was no enophthalmos or ptosis of the upper lid. The pupils reacted normally to light and accommodation. There was slight dullness to percussion over the right apex anteriorly and posteriorly with some diminution of breath sounds, but no rales were detected. An enlarged, hard, discreet lymph node was palpable in the right supraclavicular fossa.

A roentgenogram revealed definite infiltration with thickening of pleura at the right apex (Fig. 8). Temperature 101° F. Pulse 90. Respiration 24. Red blood cells 4,000,000. Hemoglobin 90 per cent. Wassermann negative. Blood pressure 100/75. Sputum negative for tubercle bacilli. Spinal tap indicated increased pressure but the cell count was normal. Neurologic examination was essentially negative.

On August 24, 1937, a biopsy was taken from the mass in the supraclavicular fossa, under local novocain anesthesia. Microscopic examination demonstrated nests of irregularly shaped cells varying greatly in size, shape and staining qualities. The cells presented large nuclei with heavy chromatin networks and prominent nucleoli. A heavy and abundant fibrous tissue stroma was conspicuous. Some areas presented marked round cell infiltration. From these sections a diagnosis of transitional cell epithelioma was made.

The patient's condition appeared unchanged following the biopsy. On the second postoperative day, after spending a comfortable night, the patient ate a normal breakfast at 7:30 A. M. At 7:55 A. M. his nurse noticed that he suddenly developed marked anorexia, that his pulse became weak and fluttering and that he rapidly sank into extremis and died within a few minutes.

At necropsy, on inspection of the body externally, it was noted that definite enophthalmos was present in the right eye. There was atrophy of the interosseous muscles of the right hand together with atrophy of the thenar group. The circumference of the right forearm was grossly less than that of the left arm, although the remaining musculature of the body was symmetrical.

On examination of the right lung and region of the thoracic inlet, a tumor, firm in consistency and yellow in color, was found to lie in an extrapleural position at the

apex of the lung. This tumor rose into the neck to the level of the fourth cervical vertebra. It had eroded the contiguous vertebral bodies and had involved the trunks of the brachial plexus as well as the stellate ganglion.

There was infiltration of the apical pleura. Careful dissection of the bronchi and bronchioles revealed nothing remarkable. Further search disclosed no other sites of possible origin for the tumor and no metastatic foci were discovered.

Microscopic examination provided further opportunity for study of the transitional cell epithelioma noted above in the biopsy. There was again observed the infiltration of the apical pleura and the subjacent lung tissue.



FIG. 8—Roentgenogram, Case 3. Showing apical shadow.

COMMENT—This case is complete with clinical and pathologic studies. The classic Haile's syndrome was present. It is interesting that the enophthalmos of the right eye was not marked until after death. In this instance, the Haile's syndrome was produced by a tumor, which by all available methods of investigation would appear to have had its origin from an extrapulmonary site in the superior aspect of the right pulmonary sulcus.

III *Symptoms*—The clinical manifestations of the "Superior Pulmonary Sulcus Tumor" are strikingly constant and, inasmuch as they are expressive of pressure-destruction effects upon structures contiguous to the pulmonary apex, they are necessarily common to a variety of neoplastic and inflammatory tumefactions occurring in this region.

Pain of an intractable type, referred to the shoulder, scapular region, axilla and down arm to fingers, is almost invariably the first symptom noted.

and precedes by several months all other signs including roentgenologic evidence of apical shadow. It is, therefore, not remarkable that the early histories, in the majority of instances, record periods of treatment for arthritis, neuritis, subdeltoid bursitis, angina pectoris and allied conditions. This symptom is next followed by a rapid and progressive loss of weight and strength accompanied by a chronic dry, irritating cough, dyspnea and cyanosis. Roentgenograms made at this time will usually reveal an early apical density, thus completing a picture which leads to a diagnosis of apical pulmonary tuberculosis. It will be noted that Case 1 of our series was so classified and received pneumothorax therapy at a tuberculosis sanatorium over a period of several months. Myosis, ptosis of the upper lid and hyperhidrosis may occur early, late or may be absent throughout, irrespective of the extent of the pathology. Hyperesthesia, anesthesia and muscular atrophies involving the arm and small muscles of the hand are variable and inconstant in occurrence. Erosion of vertebral bodies and ribs, extension of process to supraclavicular nodes and actual growth of the primary tumor into the cervical planes are later observed as the disease advances.

As has previously been emphasized, these symptoms are not peculiar to the "Superior Pulmonary Sulcus Tumor" as such, since they are merely evidence of varying degrees of pressure and destruction in the neighborhood of pulmonary apex and may, therefore, be induced by numerous conditions occurring in this region. It should, furthermore, be observed that Hare's (Horner's) syndrome is likewise nonspecific, since it has been shown to accompany various lesions affecting the apical region, whereas this sign is conspicuous by its absence in Case 1, a classic advanced type of "Superior Pulmonary Sulcus Tumor."

SUMMARY—It has been the purpose of this study to evaluate the pathologic status of the so-called "Superior Pulmonary Sulcus Tumor" and to establish the clinical significance and relationship thereto of the symptom complex variously known as Hare's or Horner's syndrome. The controversial literature pertaining to this subject has been analyzed, the history and clinical aspects of Hare's syndrome have been considered, and the clinical and pathologic aspects of the "Superior Pulmonary Sulcus Tumor" in conjunction with a carefully studied series of eight apical tumors have been submitted. It is our belief that this material presents evidence which adequately supports the following conclusions:

CONCLUSIONS

- (1) That there does exist, at the superior pulmonary apex, an epithelial neoplasm which is distinguished from all other tumors common to this region, (a) by its lack of origin from any known adjacent tissue or from metastatic foci, and (b) by a histologic picture suggestive of an embryonal source.
- (2) That the accurate identification of this tumor must be conditioned

upon (a) The exclusion of lung, pleura, ribs, periosteum, vertebrae and mediastinal structures as a source of origin, (b) the histologic proof of a squamous cell epithelioma, and (c) satisfactory demonstration of the absence elsewhere in the body of a possible focus for metastatic spread

(3) That the symptom complex, redescribed by Pancoast and known as the "Pancoast syndrome" is decidedly not a specific manifestation of the "Superior Pulmonary Sulcus Tumor" but may be induced by various types of neoplasms as well as other pathologic conditions occurring in proximity to the pulmonary apex

(4) That the syndrome attributed to Horner was fully described by Hare 31 years before Horner's publication and that therefore, it should properly be known, and is so herein recorded, as Hare's syndrome

(5) That in its early stages, this disease is almost invariably treated as arthritis, neuritis, apical tuberculosis, angina pectoris or subclavicular bursitis, and that early roentgenologic study, in obscure conditions of this type, may well bring this condition within the realm of efficient surgical therapy

(6) That roentgenotherapy has proven to be futile as a method of treatment

(7) That of eight cases of apical tumor presented, three definitely conform to the above stated conditions for identification of the "Superior Pulmonary Sulcus Tumor"

The authors desire to acknowledge their very great appreciation of the cooperation of Dr Douglas Symmers, Director of Pathologic Laboratories whose invaluable inspiration, assistance and advice proved to be a large factor in the preparation of this report

BIBLIOGRAPHY

- ¹ Pancoast, H K Importance of Careful Roentgenologic Examination in Apical Chest Tumors J A M A, 83, 1407, 1924
- Ibid Superior Pulmonary Sulcus Tumors, 99, 1391, 1932
- ² Tobias, J W Síndrome apico-costo-vertebral doloroso por tumor apicaliano Rev med latino-am, 17, 1522, 1666, 18, 57, 151, 304, 1932
- ³ Browder, J and DeVeer, A Varied Pathologic Bases for Symptomatology Produced by Tumor in the Region of the Pulmonary Apex and Mediastinum Am Jour Cancer, 24, 507, 1935
- ⁴ Evans, W A Discussion of Pancoast's¹ 1924 report, p 1411
- ⁵ Frost, T T, and Wolpaw, S E Intrathoracic Sympathicoblastoma Am Jour Cancer, 24, 483, March, 1936
- ⁶ Fried, B M Bronchiogenic Cancer Combined with Tuberculosis of Lungs Am Jour Cancer, 23, 247, 1935
- ⁷ Sergent, E Nouvelles études cliniques et radiologiques sur la tuberculose, et les maladies de l'appareil respiratoire Maloine, Paris, 1926
- ⁸ Steiner, P E, and Francis, B F Primary Apical Lung Carcinoma Am Jour Cancer, 22, 776, 1934
- ⁹ Jacob, H W Superior Pulmonary Sulcus Tumor J A M A, 103, 84, 1934
- ¹⁰ Geschickter, Chas F, and Denison, Robt Primary Carcinoma of the Lung Am Jour Cancer, 22, 776, 1934
- ¹¹ Carp, L, and Stout, A P Branchial Anomalies and Neoplasms ANNALS OF SURGERY, 87, 186, 1929

- ¹² Symmers, Douglas Personal communication
- ¹³ Terplan, K E Discussion of Paper by Clarke ¹⁶
- ¹⁴ McFarland Quoted by Pancoast ¹
- ¹⁵ Wenglowksi, Romauld Ueber die Halsfisteln und Cysten Arch f Klin Chir, 100, 789, 1912-1913
- ¹⁶ Clarke, B E Superior Pulmonary Sulcus Tumor (Pancoast) Am Jour Path, 10, 693, 1934
- ¹⁷ Fried, B M Sternoclavicular Branchioma Am Jour Cancer, 25, 738, 1935
- ¹⁸ Graef, Irving, and Stenberg, Israel Am Jour Roentgenol and Rad Ther, 36, 293, September, 1936
- ¹⁹ McCarthy, W C Quoted by Clarke ¹⁶
- ²⁰ Fulton, J F The Horner's Syndrome Arch Surg, 18, 2025, 1929
- ²¹ Hare, E S Tumor Involving Certain Nerves London Medical Gazette, New Series Vol I For the session 1838-1839, p 16-18
- ²² Colby, M F Contraction of the Pupil as a Symptom of Intrathoracic Tumors Med Chron Montreal, 6, 199, 1858-1859
- ²³ Klumpke, Mlle Contrib a l'etude des paral radiculaires du plexus brachial Rev de Med, 1885
- ²⁴ May, Bennett On Ligature of the Innominate Artery The Lancet, 1, 1064, 1886
- ²⁵ Sergent, E, and Georges, Paul Le syndrome phrenico-pupillaire Presse Med, 23, April, 1928
- ²⁶ Courcoux, A and Lereboullet, Jean Syndrome phrenico-pupillaire avec paralysie due plexus brachial dan un cas de cancer du poumon avec tuberculose associee Arch med-chir de l'app respir, 6, 569, 1931
- ²⁷ Pardal, Ramon Sindrome apico-costo-vertebral doloroso y anginoso Revista de la Asoc Med Argentina, p 913, 1932 Also to be found in El Dia Medico, 1932
- ²⁸ Pardal, R, Gerrari, R G and Itoiz, A La Semana Medica, 45, 1933
- ²⁹ Pardal, R, and Brea, Mario Cancer de apex toraco-pulmonar Revista de la Asociacion medica Argentina Sociedad de Fisiologia, T IX, 6, 98, 1934
- ³⁰ DaRin, Cornelia These Buenos-Aires, 1931 Cited by Pardal and Brea
- ³¹ Gravano, L Atenco de Clin Med del Servicio del Prof Escudero Session of June 4, 1932 Cited by Pardal and Brea ²⁹
- ³² Romano, Eyherabide, R A, and Bianchi, A E Compression medular por carcinoma originado en el pulmon Revista de la Soc de Med, 3, November, 1929

LEIOMYOSARCOMA OF THE STOMACH^{*}

REPORT OF THREE CASES

GUY W HORSLEY, M D ,

AND

R A BERGER, M D

RICHMOND, VA

FROM THE SURGICAL AND ROENTGENOLOGIC DEPARTMENTS OF ST. ELIZABETH'S HOSPITAL, RICHMOND, VA

GASTRIC LEIOMYOSARCOMA is the least common of the sarcomata which involve the stomach. The following statistics indicate its rarity in comparison with other mesothelial tumors (Table I)

TABLE I

COMPARATIVE OCCURRENCE OF VARIOUS TYPES OF SARCOMATA OF THE STOMACH

	Lympho-sarcoma	Fibro-sarcoma	Leiomyo-sarcoma
D'Aunoy and Zoeller ¹ Series 135 cases	63.0%	14.0%	9.0%
Balfour and McCann ² Series 54 cases	71.3%	13.3%	6.7%

Ewing³ states that 1 per cent of all gastric neoplasms are of smooth muscle origin. Fenwick⁴ believes the rate is about 5 per cent, while Yardunman⁵ places it at one in 300.

Benign myomata are not so rare, since 16 per cent of all necropsies (Rieniets⁶) show small tumors in the gastric wall, and, therefore, only a small percentage of these apparently undergo malignant transformation. The benign lesions, in themselves, are of little clinical or pathologic importance, unless ulceration takes place, anemia presents itself, or a malignant degeneration supervenes.

The sarcomatous lesions are described as occurring within the stomach (intra-gastric), outside the stomach (extra-gastric), or invading the wall (infiltration). Grossly, the tumors are quite innocent in appearance. The demarcation is sharp, encapsulation is apparent, and they are quite vascular, and are of a mahogany color interspersed with some yellowish portions. The intra-gastric and extra-gastric varieties are usually attached by a pedicle.

The leiomyosarcomata have been described as the least malignant of all the gastric neoplasms. Metastases are slow, usually limited, and local, though enormous nodules in the liver have been described.

There are no sex differences, the occurrence being about equal in males and females. The fourth and fifth decades of life show the greatest incidence.

The sites of predilection are usually the curvatures, the greater first,

^{*} Read before the Eastern Radiologists, Washington, D. C., February 11, 1939. Submitted for publication April 3, 1939.

followed in turn by the cardia and the lesser curvature. The pylorus is notoriously free of involvement.⁷

There is nothing particularly characteristic in the symptomatology of leiomyosarcoma. The symptoms may simulate those of ulcer, with pain as a predominant feature, which yields for a time to an ulcer regimen. The duration of symptoms is usually longer than in carcinoma. However, the loss of weight and strength is not pronounced, and nausea and vomiting are rarely present.

On physical examination, a mass is invariably palpable, which appears to be out of proportion to the patient's status of health. The tumors vary in size and masses weighing as much as 12 pounds have been reported.⁸ The size of the mass in relation to the patient's state of health is apparently one distinguishing feature, as in carcinoma greater debility would be present with a mass of corresponding size.

Roentgenologically, there is no fixed rule which may be employed in the differential diagnosis. Fluoroscopic examination offers the most information. Under the screen, movements of the gastric wall can be studied in relation to the mass, and the mucosa can be examined for pathologic involvement. In the presence of a mass producing a pressure deformity without alteration in the physiologic movements, and with no or a very shallow ulceration in proportion to the size of the mass, one should be suspicious of a smooth muscle tumor.

CASE REPORTS

Case 1—W. T. C., female, age 62, married, was admitted to St. Elizabeth's Hospital, August 6, 1937, complaining of a fulness in the chest, a mass in the abdomen, and some loss of weight and appetite. Her first symptoms had appeared two weeks before admission. Up to that time she had been feeling well and appeared to be in excellent health except for the loss of nine pounds in weight during the previous six months. Past and family histories were essentially negative. On physical examination, the patient was underweight (a small woman), dehydrated, and anemic. There was definite lagging on the right side of the thorax with dulness below the scapula. The left lung was negative. The heart was displaced to the left and downward. Blood pressure 120/80.

Abdominal examination showed a movable mass in the upper left abdomen which would descend with inspiration. There were no enlarged lymph nodes in any part of the body. The Wassermann test was negative. Hemoglobin 65 per cent (Sahli), R B C 3,300,000. The gastric contents showed an absence of free hydrochloric acid, and the combined acid was 20 to 24.

At a previous roentgenologic examination, the films of which were brought to the hospital with the patient, a diagnosis of a gastric carcinoma had been made. A review of these films suggested that something other than carcinoma was present, and another examination was advised. On the second examination the stomach was found to be deformed by an extragastric mass which apparently moved simultaneously with the stomach. No irregularities were noted in the stomach wall or mucosa, except for a pressure defect on the lesser curvature and posteriorly. The colon was similarly displaced (Fig. 1). The proximity of the tumor to the renal area suggested that it might have arisen there, so a urographic study was advised. The left kidney demonstrated no distortion either intrinsically or extrinsically.

Roentgenologic examination of the lungs revealed the right lung field to be partially obscured by fluid. There was no demonstrable evidence of metastases, and none could be found on a subsequent examination after the fluid had been withdrawn. The pleural fluid was clear, and no cause for its presence could be found either at that time or later.

Operation by Dr. J. Shelton Horsley revealed a large growth which was attached to the lesser curvature of the stomach. Because of its vascularity and the firmness of the attachment, a sleeve resection was deemed advisable.

Pathologic Examination *Gross*—The specimen consisted of about two-thirds of the stomach with the growth attached. The growth involved the lesser curvature of the

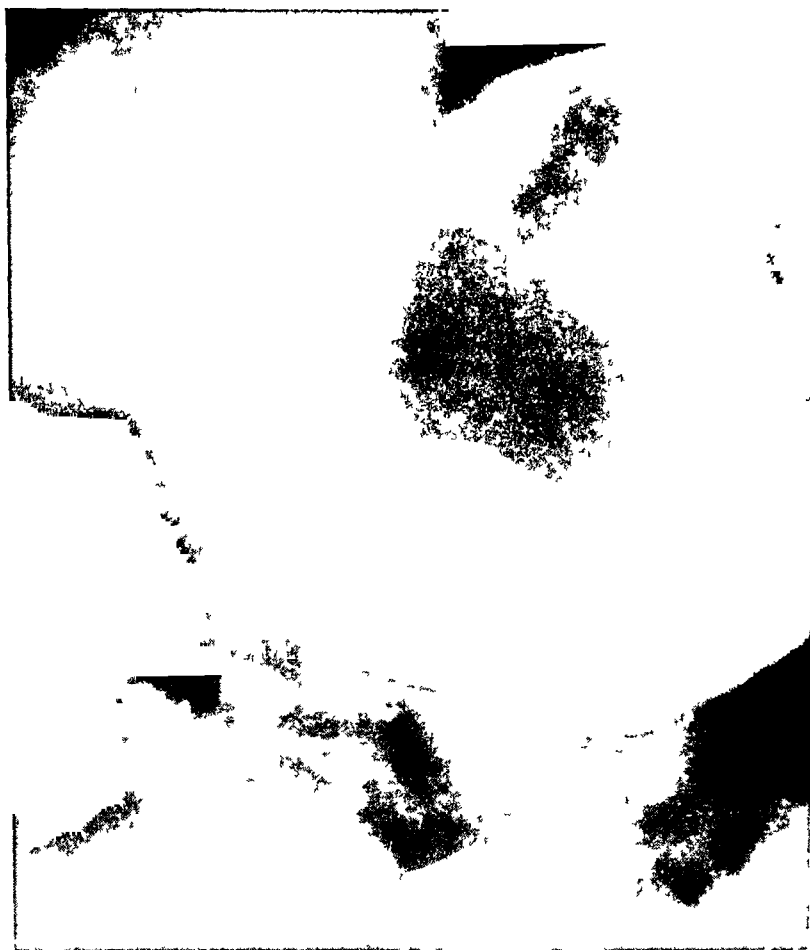


FIG. 1.—Roentgenogram of Case 1 before operation, showing no invasion of mucosa or ulceration.

stomach to which it was firmly attached. It was bosselated, but the protrusions were smooth and usually covered with peritoneum. Some portions were yellow and others were mahogany-colored. It appeared to be a solid growth, although it was rather soft in places. The growth measured 14×9×7 cm., and the entire specimen measured 12 cm. along the lesser curvature and 18 cm. along the greater curvature.

Inspection of the mucosa seemed to show that it was normal, except for a few small ecchymotic areas on the lesser curvature. On section of the growth, the tumor was solid, but was soft and had a brownish, granular-like appearance. The mucosa was not adherent, but moved freely and the growth seemed to have sprung from the muscular coat of the stomach (Fig. 2).

Microscopic—The cells were quite long, with large, oval nuclei. They were arranged in palisades, and occasionally seemed to be grouped around the blood vessels. The

GASTRIC LEIOMYOSARCOMA

nuclei were hypochromatic and contained mitotic figures The cytoplasm of the cells was scant and poorly defined There were numerous blood vessels seen throughout the sections, which apparently accounted for the dark color of the tumor No epithelial structures were found in the entire growth (Fig 3) *Pathologic Diagnosis* Leiomyosarcoma A follow-up examination of this patient, November 22, 1938, did not demonstrate any evidence of recurrence of the lesion, and the lung fields were still free from metastases or fluid

Case 2 — A P B, female, age 48, married, was admitted to St Elizabeth's Hospital, August 7, 1938, complaining of a mass in her side which had been present for several

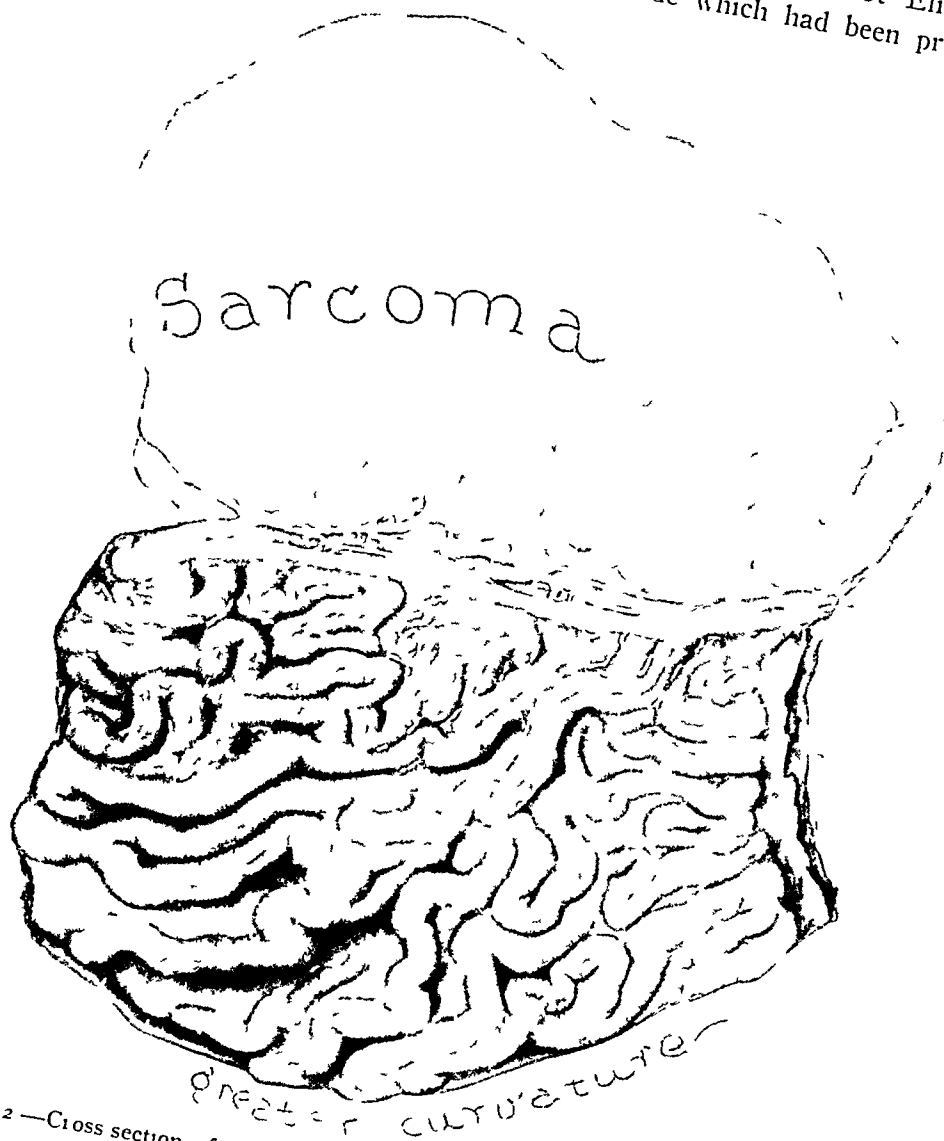


Fig 2 — Cross section of specimen from Case 1 showing its broad pedicle and no involvement of gastric mucosa

years She had paid little attention to it until recently when it became tender She sought relief chiefly for a menorrhagia and metrorrhagia The family and past histories were irrelevant Physical examination revealed the patient to be slightly underweight There was some slight distention of the abdomen, and in the upper left quadrant a movable mass was felt which seemed to be cystic The Wassermann was negative Hemoglobin 70 per cent, R B C 3,500,000

The palpable mass in this case, plus the pressure deformity of the stomach and the displacement of the colon as seen roentgenologically, should have made us suspicious of a lesion similar to that found almost a year previously in Case 1 This stomach, as in the

preceding case, showed no roentgenologic evidence of an infiltrating lesion, and no changes in the mucosa or peristaltic activity. *Clinical Diagnosis*—Extrinsic tumor.

At operation by Dr J Shelton Horsley, a large irregular tumor was found attached to the posterior wall of the stomach by a broad pedicle. The pedicle was clamped and the tumor was removed.

Pathologic Examination *Gross*—The specimen consisted of a large tumor which measured 15×11.5×12 cm. It was oval in shape and contained numerous bosselations over its surface. There were numerous lymphatic adhesions over the surface, but the tumor had a very distinct pedicle which was attached to the stomach (Fig 4). The pedicle contained all layers of the stomach except the mucosa, and obviously arose from the muscular layer. On section, there was a small necrotic area in the lower anterior

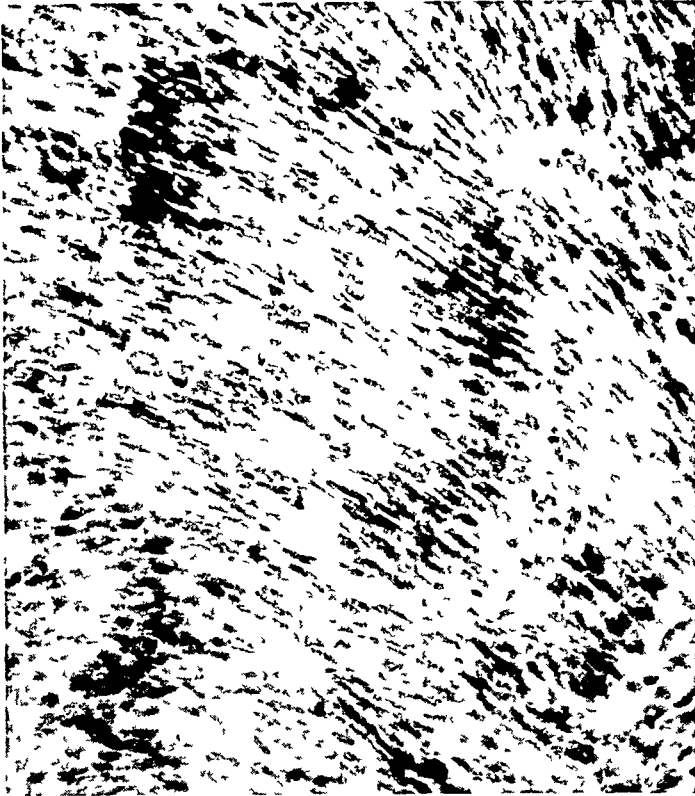


FIG 3—Photomicrograph of section from the tumor in Case 1
(×200)

portion, and the tissue seemed to be divided into lobules similar to those of a uterine myoma.

Microscopic examination showed muscular tissue, the cells being spindle-shaped with ovoid nuclei. The nuclei in this specimen were smaller than those in Case 1 and were hyperchromatic. The acidophilic cytoplasm was more prominent in this tumor and there were fewer mitotic figures noted. The cells were arranged in circles, or columns, but there was no stroma separating the cell groups (Fig 5). The growth was not as vascular and contained several areas where the tissue had undergone necrosis which was probably due to lack of proper blood supply.

The patient made an uneventful recovery, and was well when last seen by her physician a few weeks ago, six months after the operation.

Case 3—This case is from the series of Dr F Mandeville, Professor of Roentgenology at the Medical College of Virginia. The patient, L D, male, age 34, was admitted to the Memorial Hospital, Richmond, Virginia, October 25, 1938, complaining

GASTRIC LEIOMYOSARCOMA

of a mass in the abdomen. About four months previously he had had all of his teeth extracted for pyorrhea, and soon afterwards he noticed a fulness in the abdomen which became particularly apparent after eating. His capacity for food intake became greatly diminished, and about three weeks before admission he had noticed a nontender mass in the abdomen. There had been occasional nausea and vomiting. The tumor had gradually increased in size since it was first noticed, and the patient had lost about 20 pounds in weight within the past few months. There was a history of neisserian infection in 1923, and of a chancre in 1931, for which he received antiluetic treatment. The family history was irrelevant.

Physical examination revealed an undernourished, white male. There were no pal-

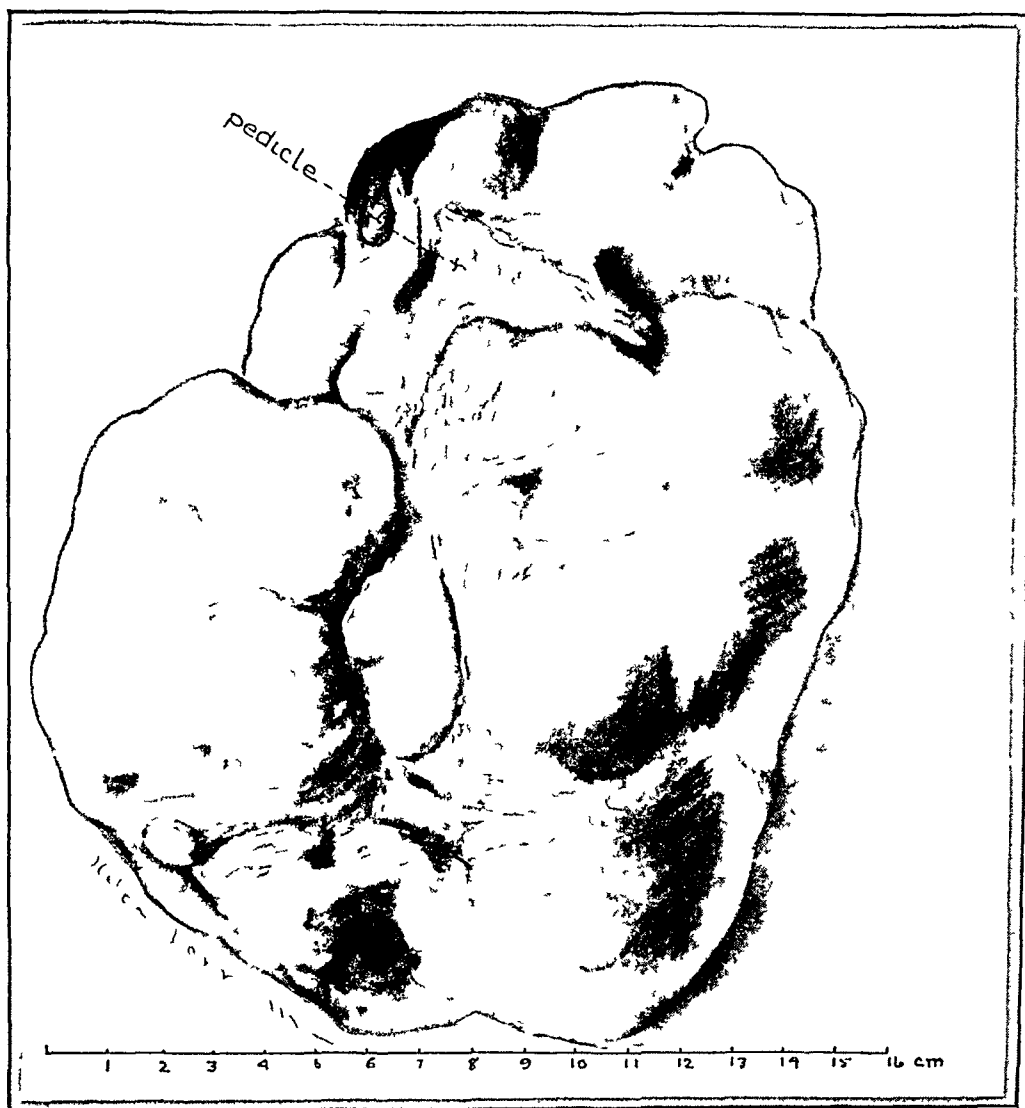


FIG 4—Drawing of gross specimen from Case 2. Note the small pedicle. There was also no involvement of mucosa in this case.

pable lymph nodes. The lower ribs on the left side were prominent and flared outward. The left upper quadrant of the abdomen presented a soft, nodular, elastic mass about the size of a grapefruit which was plainly visible. The mass would descend on inspiration. Hemoglobin 85 per cent, RBC 4,050,000, WBC 6,700.

Roentgenologic examination showed the mass in this case to be considerably larger than in the two former patients, but the findings were again quite similar. The tumor in this instance was anterior, however, but it also involved the lesser curvature. There was no evidence to suggest mural or mucosal involvement. Although an area suspicious of ulceration was seen near the cardiac end of the stomach, this was not confirmed by gastro-

scopic examination (Fig 6) In the lung fields several small metastatic nodules were visible, and a large mass was found behind the heart and just above the elevated diaphragm

Postoperative Diagnosis Sarcoma

At operation the size of the tumor prevented its removal It was partially filled with degenerated blood, and after evacuation it had a gelatinous appearance

Microscopic examination of the tissue showed a picture similar to that seen in Cases 1 and 2, except for larger nuclei with less cytoplasm The entire structure was very vascular and there were numerous blood cells in the interstitial spaces



FIG 5—Photomicrograph of section from Case 2 (×250)

The differential diagnosis in gastric sarcoma is difficult An intragastric leiomyosarcoma would not be distinguishable from a polypoid lesion within the lumen The infiltrating variety likewise would be difficult to differentiate from a linitis plastica type of stomach Carcinomata are fairly characteristic Lymphosarcoma may give a similar appearance Archer and Cooper⁹ concluded that there is no single pathognomonic sign for the latter Neither is there any for leiomyosarcoma

The cases described are of interest because of the rarity of the tumor and the associated clinical features There is a wide range in the age limit in this series and a considerable variation in the symptoms One thing is common to all three cases Each patient knew that a mass was present, one for several years, and the others for two and three weeks All three had lost some

weight, pronounced in one, but not marked in the others. The laboratory data and the physical examination, outside of the mass, offer no distinct diagnostic feature. Roentgenologically, the findings were quite similar, showing a mass producing deformities, two of which revealed no evidence of ulceration and one was only suspicious of mucosal invasion. Ulceration, if it occurs in



FIG. 6—Roentgenogram of Case 3. Note normal rugae of gastric mucosa.

leiomyosarcoma, is usually shallow and small in character, and therefore might easily be overlooked on roentgenologic examination.

Correlation of the signs, symptoms and roentgenologic findings in the three cases in this report and those described in the literature, with diagnostic criteria in mind, leads us to believe that there is no single feature or group of findings upon which reliance may be placed. A fairly long history, moderate

debility, palpable mass of variable size, with little roentgenologic evidence, except for pressure deformity on the gastric wall, may be applicable criteria for the diagnosis of gastric leiomyosarcoma

REFERENCES

- ¹ D'Aunoy, R, and Zoeller, A Sarcoma of the Stomach Report of Four Cases and Review of Literature Am Jour Surg, 9, 444-464, September, 1930
- ² Balfour, D C, and McCann, J C Sarcoma of the Stomach Surg, Gynec and Obstet, 50, 948-953, June, 1930
- ³ Ewing, James Neoplastic Diseases Saunders, Philadelphia, 1928
- ⁴ Fenwick, W S Cancer and Other Tumors of the Stomach Lancet, 1, 463, 1901
- ⁵ Yardunnian, K Primary Gastric Leiomyosarcoma Arch Path, 20, 590-595, October, 1935
- ⁶ Riemeis, quoted by Zellhoefer, H W K Proc Staff Meet Mayo Clinic, 10, No 40, October 2, 1935
- ⁷ Kessler, E Das Magensarkoma Fortschr a d Geb d Roentgenstrahlen, 50, 247-263, September, 1934
- ⁸ Kaufmann, E Pathology for Students and Practitioners Blakiston's Son and Co, Philadelphia, 1929
- ⁹ Archer, V W, and Cooper, G W Lymphosarcoma of the Stomach Diagnosis and Treatment To be published

TOTAL GASTRECTOMY FOR CARCINOMA OF THE STOMACH*

WILLIAM T LEMMON, M D ,

AND

GEORGE W PASCHAL, JR , M D

PHILADELPHIA, PA

FROM SURGICAL DIVISION "A" OF THE JEFFERSON MEDICAL COLLEGE AND HOSPITAL, PHILADELPHIA, PA

FINNEY AND RIENHOFF¹ gave Schlatter credit for having performed the first successful total gastrectomy upon man, in 1897, demonstrating that anastomosis could be successfully accomplished between the esophagus and the jejunum. They emphasized and urged correct usage of the term "total gastrectomy," pointing out that this implies nothing short of complete removal of the stomach and that the resected organ should show a portion of the esophagus on one end and a part of the duodenum on the other.

This operation affords little hope for a permanent cure but it does prolong life and adds materially to the patient's comfort. The case herewith reported lived for seven months, the greater part of which was spent in comfort. Search of the literature revealed that most of the patients subjected to total gastrectomy died within 18 months, yet Zikoff had a patient alive four years and eight months after operation, that being the longest recorded period after total gastrectomy. Mayo, Allen² and others report patients having lived as long as four years. A moderately large number of successful cases that have lived as long as three years have been reported. Many of these patients were returned to varied useful activities and were spared an inevitable earlier death only by having been subjected to the operation. It is difficult to make an accurate report on the number of total gastrectomies that have been performed. In recent years, the operation has been attempted more frequently but, undoubtedly, all cases have not been reported. In 1933, Roeder³ reported 88 cases of total gastrectomy which had been performed up until that time. This record included three cases of his own, and is possibly the most accurate and comprehensive study that has been presented. There was a primary operative mortality rate of 50 per cent among these 88 patients, the percentage being based upon the patient living as long as two months after operation. He reports only 44 successful cases of total gastrectomy. Doctor Lahey⁵ reports eight total gastrectomies at his clinic, the last five of which have been successful.

Peritonitis and "shock" were predominating factors in early deaths.⁴ The peritonitis was more frequently the result of leakage than from soiling. This can, quite reasonably, be avoided by proper utilization of the peritoneum surrounding the esophageal orifice. Adrian Verbruggen⁶ reported a study of the intramural extension of gastric carcinoma cells, and showed that at least four

* Read before the Philadelphia Academy of Surgery, January 16, 1939. Submitted for publication March 17, 1939.

centimeters of apparently healthy stomach beyond the limits of the lesion should be removed with the primary growth. To follow this procedure in carcinoma or suspicious ulcers, would necessitate complete removal of the stomach in many cases of lesser curvature involvement. Wide resection is important to secure a sound area for anastomosis. In the case herewith reported, the lower part of the esophagus was infiltrated with the cancer and the thoracic esophagus had to be drawn downward about seven centimeters in order to secure a healthy area for anastomosis. One of our cases of subtotal resection for gastric carcinoma of the lesser curvature and posterior wall died 15 days following operation because of degeneration of the tissue and leakage of the posterior suture line. At autopsy, we concluded that total gastrectomy should have been performed and would have afforded a greater opportunity for success.

Hemorrhage probably accounted for some of the deaths attributed to "shock." A pulmonary complication in these patients of minimal resistance practically removes hope for a favorable result. The use of a high spinal analgesic with a prolonged action greatly enhances the possibility of success and aids in avoiding shock and pulmonary complications. We were able to maintain our patient in satisfactory condition throughout operation by giving adequate amounts of glucose in normal saline by continuous venoclysis. We believe this to have a definite place during such operations.

Recurrence of the malignancy is responsible for most of the deaths subsequent to operation.⁵ Our patient died seven months after operation from this cause. Anemia can be prevented and seems to present no special problem. Our patient was found to have a greater number of erythrocytes seven months after gastrectomy than she had beforehand. She had received only one blood transfusion of 400 cc., and that postoperatively, and at intervals had been given iron, liver and hydrochloric acid.

Case Report—I. W., female, age 63, was referred to Doctor Lemmon's Service at the Bellevue Hospital, Camden, N. J., by Dr. Maurice Baker on May 5, 1938. Her complaints began about six months previously, when she noticed some difficulty in swallowing. Nausea and vomiting occurred intermittently for a time but for the three weeks preceding admission had been persistent, even after taking water. She had been troubled with a vague and painful discomfort across the epigastrium but, strangely, was free of distress on admission. Since December, 1937, she had lost 22 pounds in weight and now felt very weak and tired. Her mental attitude was poor.

Studies revealed 4,070,000 red cells, leukocytes 9000, hemoglobin 90 per cent. The urine was alkaline and showed a faint trace of albumin. An earlier gastric analysis, made by Doctor Baker, showed total acidity 7, free hydrochloric acid 3, blood absent. A mass was palpable in the epigastrium. A roentgenologic diagnosis of extensive gastric carcinoma (Fig. 1) was made March 3, 1938, by Dr. E. E. Downs.

Operation—May 7, 1938. Under spinal analgesia (200 mg. novocain in second lumbar interspace) the abdomen was opened through an upper right rectus incision. Exploration showed the stomach to be completely involved with carcinoma of the linitis plastica type. The lymph nodes along the curvatures were not palpable. No evidence of metastasis to the liver, spleen or elsewhere was seen or felt. Total gastrectomy was elected as the only procedure offering the patient any hope of temporary or permanent relief.

Operative Procedure—The blood supply was doubly ligated on both curvatures, beginning at the duodenum and extending to the esophagus, leaving as much omentum as possible attached to the stomach, in order to include the regional lymph nodes. The freed and mobilized first portion of the duodenum was divided between clamps with cautery. The distal end was invaginated with a Connell stitch followed by purse-string sutures and reinforced by an omental graft.

The free distal portion of the stomach was covered with gauze and traction made downward. A flap of peritoneum was reflected from the diaphragmatic surface anterior to the esophagus, to be used later in the anastomosis. At this time the lowermost part



FIG 1—Roentgenogram six weeks before operation, showing extensive involvement of the stomach by carcinoma.

of the esophagus was found to be infiltrated by the lesion. About seven centimeters of the thoracic esophagus was drawn downward and freed, care being taken to avoid injury to the vagi nerves, the esophageal vessels and pleura. By traction on and rotation upward of the stomach, the posterior wall of the esophagus was exposed. A loop of jejunum about two feet from the duodenojejunal junction was selected and carried upward, in front of the colon, and brought in apposition with the posterior wall of the esophagus and fixed to it by several interrupted linen sutures which were so placed as to maintain the normal caliber of its lumen. A continuous linen suture was inserted approximating the esophagus and jejunum. The field was carefully packed off with gauze and the esophagus was incised parallel with one-half centimeter from the suture line, the contents being carefully aspirated as soon as the esophagus was opened. An opening of equal size was made in the jejunum. A posterior row of continuous locked sutures of No 0 chromic catgut was inserted, approximating the posterior mucosal edges. Several interrupted sutures were used to secure hemostasis. The remaining anterior wall of the esophagus was divided, removing the stomach. The anterior edges were approximated with a Connell

stitch, this suture being a continuation of the inner, posterior row of sutures. The outer or posterior continuous suture was then continued anteriorly forming the second or outer anterior row. The previously reflected peritoneal flap was now sutured, by interrupted stitches, to the jejunum at the line of anastomosis. This gave a serosa-to-serosa apposition. The jejunum, on each side of the anastomosis, was fixed to the parietal peritoneum by interrupted linen sutures, thereby relieving tension on the anastomosis.

A jejunojejunostomy was performed about 14 inches from the anastomosis. The abdomen was closed in layers without drainage.

The operation was begun at 9 15 A M and ended at 12 15 P M. She received as a supplement to the spinal analgesic, which was effective for one hour and 15 minutes, 12 ounces of ether by open drop. During the course of the operation she had 2,000 cc 10 per cent glucose by venoclysis. Her condition was good throughout the operation and she left the operating table with a pulse of 110, respiration 32, blood pressure 135/85.



FIG 2—Photomicrograph of a section of the stomach showing adenocarcinoma of the limitis plastica type. The infiltration of the various layers of the stomach by cancerous cells can be seen ($\times 7$).

The mucosa is thickened and thrown into folds. No definite ulceration is observed. There are several, slightly enlarged, firm lymph nodes, attached to the fat on the external surface.

Histologically, sections from the wall of the stomach reveal a diffuse infiltration of all the coats by clumps of epithelial cells and also extensive inflammatory reaction and

Pathologic Examination—Gross. Dr B L Crawford: "Specimen consists of entire stomach which has been fixed, and measures 16 cm from cardia to pylorus, along the lesser curvature. The wall is markedly thickened and indurated, the wall averaging from 1.5 to 2 cm in thickness.



FIG 3—Photomicrograph showing the invasive infiltrating nature of the cells in the limitis plastica type of adenocarcinoma ($\times 100$).



FIG 4—Photomicrograph of a regional lymph node showing metastasis ($\times 100$).

fibrosis. The mucosa is not completely destroyed in most areas, but is largely replaced by the infiltrating tumor cells. The tumor cells also replace much of the musculature. The enlarged lymph nodes contain many clumps of infiltrating epithelial cells.

Pathologic Diagnosis: Diffuse adenocarcinoma of the stomach, leather-bottle type, with metastasis to the regional lymph nodes (Figs 2, 3 and 4).

The patient had a strikingly smooth convalescence, her fluid balance and nourishment being maintained by venoclysis and one blood transfusion of 400 cc of citrated blood. On the fourth day she took fluids by mouth. On the sixth day she was given semisoft food with no ill effect. She was discharged on the twentieth postoperative day, having repeated hunger sensations which were satisfied by frequent, small feedings of a varied diet which caused no digestive distress.



FIG 5 —Roentgenogram made five months after gastrectomy. Barium can be seen in the esophagus and upper small bowel.

Subsequent Course—At home, she gained eight pounds and performed household duties. Anemia was controlled by administration of liver, iron and hydrochloric acid. In September, 1938, she began to complain again of difficulty in swallowing and on September 20, Dr. Louis H. Clerf, at the Jefferson Hospital, inspected the esophagus. He found that it "appeared normal until the lower end was reached, at this point the mucosa was inflamed, along the anterior and left lateral wall it was moderately edematous and thickened. No ulceration observed. Nothing found to suggest neoplasm. The lumen was narrowed but with the aid of a bougie it was possible to pass an esophagoscope which had an external diameter of about one centimeter. The mucosa of the food passageway beyond the end of the esophagus was intensely red." He remarked, "The narrowing may be due to malignancy or cicatricial changes. There was nothing noted, however, to suggest

that the process was malignant in origin. I would suggest that dilatation be carried out at intervals of one to two weeks for a time using an olive-tipped bougie passed over a previously swallowed string." This narrowing responded to dilatation. Roentgenologic examination at this time revealed a functioning stoma without obstruction (Fig 5). Dilatation was done at intervals with relief, but in late November, 1938, when she was unable to retain anything by mouth, a second operation was necessary.

On her second admission, she had lost more weight than she had gained. Her skin was dry and loose from marked dehydration and malnutrition. Erythrocytes 4,200,000, leukocytes 14,200, hemoglobin 81 per cent. After four 400 cc blood transfusions, she had an erythrocyte count of 4,760,000 and a hemoglobin of 90 per cent. She had also received a considerable amount of glucose and fluids by venoclisis to combat dehydration and aid nutrition.

The second operation, December 4, 1938, revealed diffuse metastatic carcinomatosis with multiple intestinal obstructions. The liver, even now, showed little involvement grossly. A jejunostomy was performed. The patient died, December 7, 1938, seven months after the removal of her stomach.

We believe, with Dr Frank H Lahey, of Boston, that the proper conservation and utilization of the peritoneal flaps adjacent to the esophagus is one of the most important factors in preventing leakage at the site of anastomosis. We wish to call attention to the sustained normal erythrocyte count. It is of interest to note that this unanticipated operation was performed through a right rectus incision, that no Levine tube was employed either during or after operation, due to the patient's absolute refusal to have it passed, that the anastomosis was accomplished without clamps, that no jejunostomy was performed, and that it was the operator's first complete gastrectomy. The patient was comfortable and entirely free of complaints for a period of six months during which she enjoyed eating, gained weight and had a useful existence.

REFERENCES

- ¹ Finney, J. M. T., and Rienhoff, W. F., Jr. Gastrectomy. Arch Surg, 18, 140-162, January, 1929.
- ² Clute, Howard M., and Albright, Hollis L. Total Gastrectomy for Cancer. Am Jour Surg, 35, 56-63, 1937.
- ³ Allen, Arthur W. Carcinoma of the Stomach. With Special Reference to Total Gastrectomy. ANNALS OF SURGERY, 107, 770-782, May, 1938.
- ⁴ Roeder, C. A. Total Gastrectomy. ANNALS OF SURGERY, 98, 221, 1933.
- ⁵ Lahey, F. H. Complete Removal of the Stomach for Malignancy. Surg, Gynec, & Obs, 67, 213-223, August, 1938.
- ⁶ Verbrugghen, Adrian. Intramural Extension of Gastric Carcinoma. Proc Staff Meet Mayo Clinic, 6, 765-768, December 30, 1931.

PERFORATIONS OF THE GASTRO-INTESTINAL TRACT*

HERBERT WILLY MEYER, M D

NEW YORK, N Y

FROM THE SURGICAL SERVICE OF DR. CARL FICHERS, LENOX HILL HOSPITAL, NEW YORK, N Y

PART TWO

Traumatic Perforation of Stomach and Duodenum—In our series, there was only one case of traumatic percutaneous perforation of the stomach. This occurred in a woman, age 31, who shot herself through the epigastrium in an attempted suicide. She was admitted to the hospital but died before she could be operated upon. Autopsy revealed an hemoperitoneum with retroperitoneal hemorrhage, tearing of the liver, perforation of the stomach and laceration of the pancreas, spleen and left kidney.

If patients do not succumb immediately to external injury with shock and hemorrhage, they must be considered as a surgical emergency, and an exploratory celiotomy must be performed immediately.

Retroperitoneal rupture of the duodenum, after external violence to the upper abdomen, must be included in the differential diagnosis. The clinical picture differs from intraperitoneal rupture, and a thorough exploration of the duodenum is indicated. The mortality is high if the perforation is not closed early. Frost and Guy³⁰ reported two cases of multiple perforations of the duodenum. One was caused by external violence and was unrecognized at the time of operation, the other was the perforation of separate duodenal ulcers, which perforated either simultaneously or within a period of eight hours. At operation, the second opening was discovered because of the persistent leakage of fluid after the closure of the first perforation.

In our series there were two patients, each of whom had two duodenal ulcers. One case had two perforations of separate ulcers, 22 months apart. Another case died after operation and at autopsy showed a diverticulum of the duodenum and two ulcers, one of which had perforated. Diffuse peritonitis was present.

PERFORATION OF THE SMALL INTESTINE—The mortality of perforation of the small intestine is high. In our series of 16 cases, ten died (62.5 per cent) and six recovered. Intestinal rupture occurs by crushing, tearing or bursting of the intestine. Crushing occurs by a blow against the abdominal wall with crushing of the intestine against a fixed structure. Tearing is caused by a tangential blow which severs the intestine from its attachments, the tear going into the bowel or into the mesentery. Bursting is due to fluid or gas caught in the bowel as in a strangulated hernia. Perforation can also result

* Read before The New York Surgical Society, March 1, 1939. Submitted for publication February 12, 1939.

from the erosion of an inflammatory process such as an ulcer (tuberculous, typhoid, marginal or simple) or segmental enteritis or diverticulitis Typhoid fever ulcers of the small intestine may perforate with sudden onset and all signs of an acute emergency The nine pathologic conditions preceding perforation in our series are listed in Table XXVI

TABLE XXVI

ETIOLOGIC FACTORS OF PERFORATIONS OF THE SMALL INTESTINE

Disease	Cases	Operation	Result	Cause of Death	Autopsy
Tuberculous ulcer	2	1 Suture	Died 2	Peritonitis 2	2
Typhoid ulcer	2	1 Suture	Died 2	Peritonitis and disease	1
Marginal ulcer	2	2	Cured 2		
Strangulated hernia	1	1	Died 1	Peritonitis	
Jejunal ulcer	1	1	Died 1	Peritonitis	1
Diverticulitis	1	1	Died 1	Peritonitis	1
Meckel's diverticulum	1	1	Cured 1		
Segmental enteritis	2	2	Died 1	Peritonitis	1
			Cured 1		
Traumatism	4	3	Died 2	Peritonitis	2
			Cured 2		
Totals	16	13	10 Died, 6 Cured	Mortality 62 5%	8

ABBREVIATED CASE REPORTS OF PERFORATIONS OF THE SMALL INTESTINE

Perforation of Tuberculous Ulcers

Case 1—P B, age 64, had had signs of pulmonary tuberculosis with shortness of breath for two years, and pleurisy He was admitted to the hospital with a possible diagnosis of lung tumor which was confirmed by bronchoscopy The patient went steadily downhill and died ten days after admission The autopsy findings were active pulmonary tuberculosis, pneumonia of the right lower lobe, myocardial degeneration, marked tuberculous enterocolitis and perforation of a tuberculous ulcer of the ileum, one inch from the ileocecal valve

Case 2—C L, age 76, had been operated upon for an appendiceal abscess nine months before admission The appendix was removed and an opening in the ileum was closed, and the operative wound never healed He was admitted later, with the complaint that his bowels had not moved for eight days The abdomen was distended and tender He was operated upon for a diffuse peritonitis, with closure of a perforation of the ileum He died the day following admission and at autopsy a tuberculous enteritis with perforation was found with a fibrinopurulent peritonitis

Perforation of Typhoid Ulcers

Case 3—H F, age 36, had been ill for three weeks with typhoid fever The night before admission he suddenly experienced severe pain in the left lumbar region radiating to the right lower quadrant, due to perforation The temperature was 102.2°F, pulse 80, W B C 7,600, polymorphonuclear leukocytes 62, eosinophils 1 At operation, the last six to eight feet of the small intestine were found to be red, with a granular surface Two perforations, 18 inches from the ileocecal valve, were closed with purse-string sutures A number of other bluish, indurated areas were seen in the lower ileum and cecum The patient died on the fifth postoperative day, with a temperature of 107.2°F, and a pulse of 150

Case 4—H G, age 33, six days before admission had had a severe attack of headache On the third day of his illness he had a severe epistaxis On admission, his ab-

domen was slightly distended, soft and tender. The liver and spleen were not palpable. Four days after admission he had a severe intestinal hemorrhage. Three days later there was suspicion of a perforation. A surgical consultation was held but it was thought that no perforation was present. The patient died ten days after admission. Autopsy showed perforation of the ileum, four inches from the ileocecal valve.

Perforation of Marginal Jejunal Ulcer

Case 5—P. O., age 44, suddenly experienced severe pain in the epigastrium which continued for six hours, until admission. Two and one-half years previously, he had had simple closure and gastro-enterostomy for a perforated gastric ulcer. He had pain after eating. On admission, there was rigidity of the upper abdomen, absence of liver dulness, and a diagnosis of perforated ulcer was made. At operation, there was greenish, turbid fluid and gas in the abdomen. A perforation of the jejunum just opposite the gastro-enterostomy was found. This was closed and the patient made an uneventful recovery.

Case 6—J. O., age 43, had "stomach trouble" for ten years. He had had a perforated gastric ulcer which was operated upon elsewhere. Upon admission, a posterior gastro-enterostomy was performed, and a mass of scar tissue was found at the pylorus, adherent to the liver and infiltrating the pancreas. Roentgenologic examination had shown no evidence of retention. Following this, he was well for eight and one-half years, when he developed hunger pain, which continued to disturb him for 18 months. Sixteen hours before admission, he felt a severe "doubling-up" pain all over the abdomen. On admission, the abdomen was distended and board-like. At operation, purulent material was found in the peritoneal cavity. A perforated jejunal ulcer was found at the site of the gastro-enterostomy which had to be separated. An end-to-end anastomosis of the jejunum was performed. A jejunocolic fistula was also repaired. As the pylorus was open—this was demonstrated by passing a finger through it—the stomach was closed. Recovery was uneventful, but the patient died five months later from pulmonary tuberculosis.

Perforation of a Strangulated Hernia

Case 7—D. C., female, age 54, had a femoral hernia for 20 years. This became strangulated a few hours before admission. She was operated upon immediately and perforation of the ileum, with generalized peritonitis, was found. The loop of intestine was exteriorized and the abdomen drained, but the patient died 12 hours later.

Perforated Jejunal Ulcer

Case 8—M. R., male, age 55, had diarrhea for 11 months, passing ten to 20 stools daily. He had lost 35 to 45 pounds in weight, and had been weak for the past seven months, during which time he had an occasional fever up to 104°F. There was pain in the right upper chest of seven weeks' duration. Cholecystostomy had been performed in 1928, at which time diabetes developed. Three years later cholecystectomy was performed. A provisional diagnosis of colitis and possible pernicious anemia, was made. The hemoglobin was 30 per cent, R. B. C. 1,500,000, W. B. C. 4,200. The polymorphonuclear leukocytes were 52 per cent. The spleen was palpable. Sepsis was suspected. The patient had high temperature.

One month after admission to the Medical Service, he developed an acute abdomen, which suggested perforation. He was operated upon and a large perforation of the small bowel was discovered. The abdomen was drained but the patient died.

At autopsy there were a number of interesting findings. Mesenteric thrombosis with pulmonary emboli, acute congestion of the lungs, spontaneous perforation of the jejunum with generalized peritonitis, acute enterocolitis, marked lymphoid hyperplasia of the jejunum and ileum. Plaques were found in the first three feet of the small intestines. Six inches from the duodenojejunal juncture a perforation was found, probably of one of

the plaques seen on the mucous membrane of the intestine. Microscopic examination showed marked proliferation of the reticulum of the lymph follicles with almost complete destruction of the normal architecture, and scattered throughout were larger and smaller, irregular giant cells, usually with a single nucleus. The dominant cells remained as a small lymphocyte. Patches of similar histologic character were found on the serosa of the small intestine. There were peritoneal and mediastinal lymph nodes—the same histologic picture as described in the intestine—with destroyed normal architecture and marked increase of the reticulum. Here and there were smaller areas of necrosis and the presence of giant cells that did not resemble Dorothy Reed cells. Scattered throughout the nodes were vascular thrombi, some recent, some of longer duration. Areas of coagulation necrosis were in close proximity to these vascular thrombi.

Gerster³¹ recently published an exhaustive study of 128 reported cases of jejunal diverticula found in the literature. This article was written on the basis of a case which he had operated upon and which is included in our series, abstracted and reported herewith.

Perforation Due to Diverticulitis

Case 9—T. A., age 51, was seized with severe pain in the lower abdomen on the day of admission. There was rigidity throughout the entire abdomen and tenderness mainly in the left lower quadrant. Temperature 102.4°, pulse 100, W. B. C. 8,400, and 78 per cent polymorphonuclear leukocytes. At the time of operation a loop of jejunum was found about 12 inches from the duodenojejunal juncture, which was apparently the cause of the peritonitis. In this portion there were eight distinct diverticula with no gross evidence of perforation, at the time of operation. At autopsy, however, perforation of the lowermost diverticulum, at the right-hand side of the mesentery, was found. There were six diverticula, measuring from 3 to 6.5 cm., three on the left and three on the right side of the mesentery, the total area representing 80 cm. of the small intestine. There was acute dilatation of the stomach, duodenum and jejunum as far as the region of the perforation.

Perforation of Meckel's Diverticulum

Case 10—R. K., age 27, had generalized abdominal cramps for six hours, with vomiting, fulness in the abdomen and cramp-like pains every 30 minutes. The bowels had moved. There was spasm and tenderness 2 cm. below McBurney's point. W. B. C. 15,000, 90 per cent polymorphonuclear leukocytes, temperature 100.2°. The patient was observed with an uncertain diagnosis. The leukocytes dropped to 7,000 but the polymorphonuclear count remained at 90 per cent. Roentgenologic examination of the abdomen showed signs of obstruction. The patient was operated upon the third day after admission and a perforated Meckel's diverticulum was found, with intestinal strangulation due to a ring formed by the diverticulum and a band. The patient had a very serious and stormy convalescence, complicated by pneumonia, but eventually recovered.

Perforation Due to Segmental Enteritis

Case 11—A. D., age 54, had three attacks of abdominal pain, with loss of weight and blood in the stool during the past two years. One week before admission, he suffered another attack, in which the abdomen became rigid and moderately distended. There was marked tenderness in the left lower quadrant and a sausage-like mass could be felt in the lower abdomen. W. B. C. 7,000, polymorphonuclear leukocytes 79 per cent, temperature 102.6° F., pulse 144. At operation, a small perforation of the ileum was found approximately 6 cm. from the ileocecal valve, where there was a gangrenous area about 4 cm. in length. This area was drained, but the patient died two days after

operation Autopsy revealed segmental enteritis, measuring 35 cm in length, proximal to the ileocecal valve

Case 12—W W, age 28, had been admitted two years previously, for an ulcer of the stomach, having had abdominal symptoms for three years Two days before the present admission, he had severe, generalized lower abdominal pain The lower abdomen was slightly tender, most marked in the right lower quadrant W B C 19,400, 87 per cent polymorphonuclear leukocytes, temperature 99.6°F, pulse 88 At operation, all the organs in the pelvis were found very adherent There was a tumor mass 6x4 cm, but no gross perforation could be discovered, although an infiltration was present at the site of the tumor mass in the small intestine, which was drained Roentgenologic examination had shown segmental enteritis for the terminal 12 inches of the small intestine (Fig 5) The patient made a satisfactory recovery A secondary ileocolostomy was performed six weeks after drainage of the peritoneal abscess, following which the patient made a satisfactory recovery

Traumatic Perforation—Subcutaneous injuries of the abdomen occur in the following order of frequency Liver, spleen, kidneys, intestine, stomach, bladder and pancreas The intestine was involved in 11.1 per cent of all cases in Geill's series³² In children, perforations of the small intestine are not very common Beekman³³ reported two cases, occurring in 59 children admitted to Bellevue Hospital with abdominal injury Siegel³⁴ studied 376 cases, in whom operation had been performed, and showed that the mortality increased as the time between injury and operation increased, namely, 15.2 per cent within the first four hours, 44.4 per cent within five to eight hours, 63.6 per cent within nine to 12 hours, and 70 per cent after 12 hours

Treatment of the initial shock is of the utmost importance Counsellor³⁵ advises administering 6 per cent solution of acacia intravenously Leakage from small intestinal perforation in the early hours is rare and, therefore, peritonitis does not occur early Lack of peristalsis and contracture of the circular muscle fibers and prolapse of the mucous membrane act as a plug to the perforation If the patient is in shock, treatment should be first instituted for shock and then operation performed If there is no shock, operation should be performed early, and should be as simple as possible Long resections of the intestine should be avoided The intestine should be examined for its entire length, starting at some fixed point, such as the ileocecal region Inlow³⁶ has shown that perforations of the small intestine following trauma may occur late

Secondary perforation results from the necrosis and sloughing of an area of the intestinal wall on the antimesenteric border which has been contused, generally, either from a direct blow over the midportion of the abdomen or from crushing Intestinal distention is a contributing factor Perforation occurs most frequently about two weeks after the injury The initial symptoms are those of abdominal trauma in general After apparent recovery, there are symptoms in the intermediate stage suggesting the possibility of late perforation These are recurring pain and tenderness, vomiting, meteorism, diarrhea, and blood in the stool The pain of the perforation is similar to that

accompanying a perforated gastric ulcer. A fulminating and rapidly fatal peritonitis results. The prognosis of simple intestinal contusion is good. Most heal without being diagnosed. When necrosis occurs, however, all reported

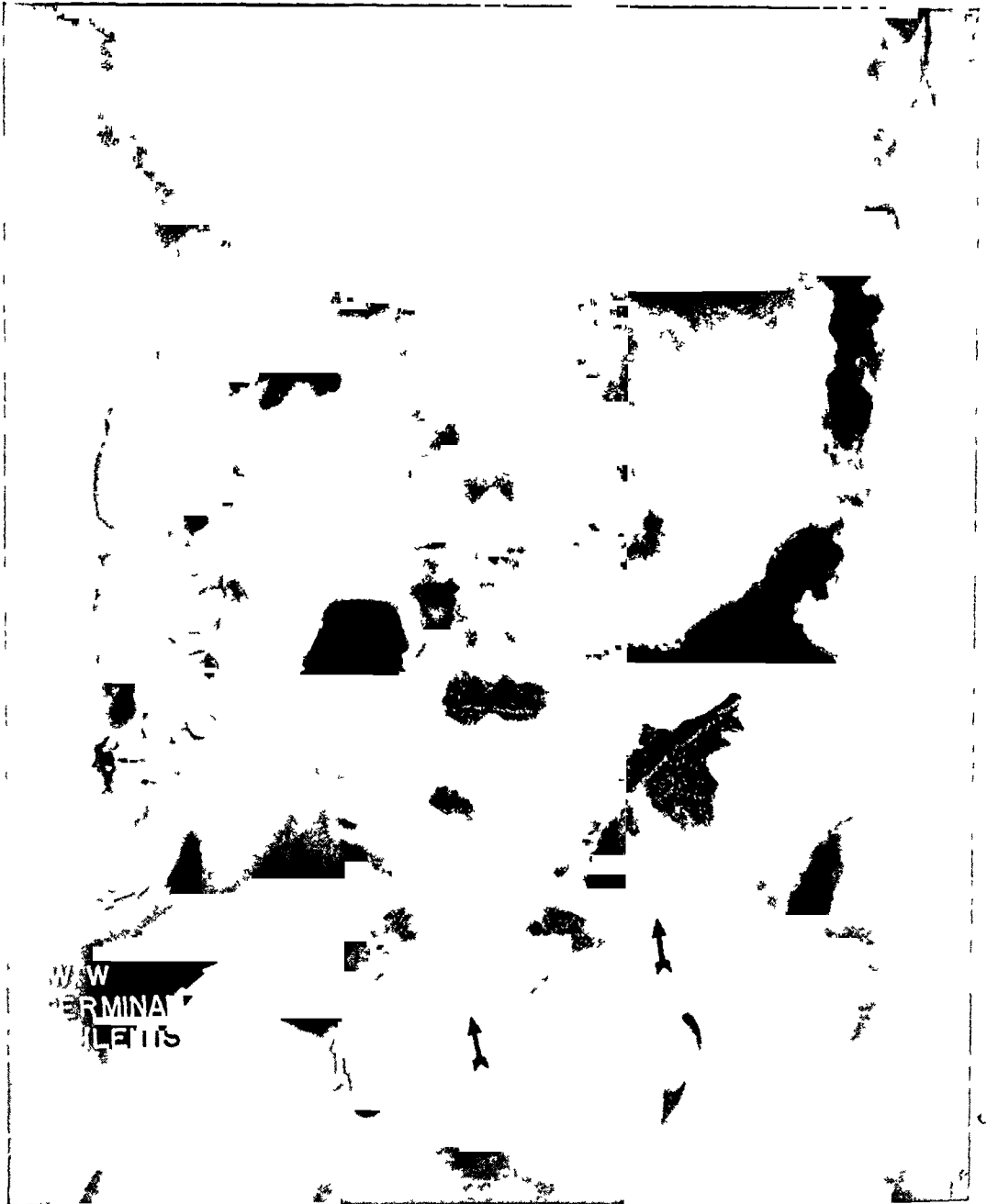


FIG 5—Case 12, W W. Roentgenogram showing terminal ileitis which had perforated

cases have proven fatal. The initial treatment is that of abdominal trauma in general. If visceral injury is suspected, exploration should be performed at once. Areas of contusion should be protected by being turned in, if very small, or covered with omentum or sutured to the parietal peritoneum, if large. Primary resection is required only occasionally. In the intermediate stage, perforation may be guarded against by careful dietary regimen with

periods of absolute withdrawal of food if necessary. Patients should be kept in the hospital until the critical period is past.

In our own series there were four cases of traumatic rupture of the small intestine. Three were operated upon, two recovered and one died. The fourth case was discovered at autopsy. Both cases that died were autopsied.

Traumatic Perforation of Intestine

Case 13—T. M., age 21, was thrown from the end of a truck ten minutes before admission to the hospital. The abdomen struck against the tail board of the truck. The patient was in acute pain. There was rigidity of the abdomen and exquisite tenderness, especially on the left side. He was operated upon immediately, and a perforation of the ileum was found, the size of a dime. The perforation was sutured, the abdomen closed, and the patient made an uneventful recovery.

Case 14—C. B., age 23, while playing ball, half an hour before admission, ran into a stone stoop, hitting abdomen and head. He fell to the ground. On attempting to rise, he fell again, aware of a dull heavy pain in the abdomen and a desire to move the bowels. He was admitted 30 minutes later. He was in acute pain and in shock. Respirations were rapid and labored, pulse 124. There was abdominal rigidity and tenderness to the left of the umbilicus. There was flatness on percussion of the entire left side and lumbar gutter, with no apparent movement on respiration. There was a small skin contusion to the left of the umbilicus. Catheterization showed clear urine. Rectal examination was negative. W. B. C. 14,000, polymorphonuclears 88 per cent, temperature, 99.2°F, pulse 120. As soon as the patient had overcome the initial shock, he was operated upon. The pelvis was found full of semifluid blood. Fibrin was present on the surface of the coils of the small intestine which were covered by omentum. When this was turned upward, a tear in the intestine on the left side of the abdomen was found, one-half inch long, opposite the mesenteric attachment. This was sutured in two layers, the abdomen was closed, and the patient made an uneventful recovery.

Case 15—F. G., age 18, was admitted in coma, having been struck by a taxicab while roller skating. He was in shock. There was a laceration of the right supra-orbital region and multiple contusions of the right side of the abdomen, subconjunctival hemorrhage of the right eye, and no abdominal rigidity. A spinal tap was done and blood found. The patient died 24 hours after admission with a temperature of 105°F, pulse 130. At autopsy, a contusion and abrasion were found in the right groin. There was a suppurative peritonitis. The intestines were perforated in four places over an area one and one-half feet long. The perforations measured from 0.5 to 1.5 inches in length, and were near the mesentery or opposite it. *Cause of Death* Ruptured intestine and acute, suppurative peritonitis.

Case 16—J. S., age 42, was hit by a taxicab and thrown to the ground. He was brought to the hospital unconscious. There were areas of ecchymoses, three inches in diameter, around the umbilicus. Operation was performed and free blood and clots were found in the peritoneal cavity. Thirty inches of the small intestine were torn away from the mesentery. This began three inches from the ileocecal junction, and at another point, considerably higher up, a tear was found opening into the intestinal lumen. Both areas were resected. An ileocecostomy and an entero-enterostomy were performed. The patient died two days after operation, with a high temperature. At autopsy the cause of death was laceration of the mesentery, acute suppurative peritonitis and bronchopneumonia.

Intestinal Perforation Due to Carcinoma—Perforation of gastro-intestinal malignancies can hardly be classed as an emergency, since it is usually known that the patient is suffering from carcinoma. Perforation occurs late in the course of the disease and death invariably follows. We had four cases of this

type and autopsy in each instance proved the diagnosis of perforation of a malignant tumor. One case occurred a year after the successful resection of an esophageal carcinoma. There was recurrence in the lower stump, at the stomach, with perforation into the peritoneal cavity. Another case of recurrent carcinoma of the stomach and colon had signs of obstruction. A cecostomy was performed and at autopsy a perforation of the tumor of the transverse colon was demonstrated. One other case of perforation of a carcinoma of the rectum, with peritonitis, was proven at autopsy. The fourth case was one of carcinoma of the sigmoid, with resulting peritonitis. It was diagnosed. At autopsy, multiple perforations of the sigmoid were demonstrated with involvement of the small intestine. Occasionally it may be possible that a tumor may perforate without previous knowledge of its presence.

Turner³⁷ reports an unusual case of perforation of a carcinoma of the jejunum.

Case Report—Doctor Turner³⁷ The patient a woman age 65, had had recurrent colicky attacks of pain for six months. These occurred at irregular intervals and were not accompanied by vomiting. She had lost some weight. Then she experienced sudden severe pain on the left side accompanied by vomiting. The left abdomen was rigid and tender. On admission, no swelling could be appreciated. Pulse 84, temperature 99.4° F. *Clinical Diagnosis* Urinary calculus. Roentgenologic study was however negative. Vomiting recurred and the abdomen became rigid. Under anesthesia a mass could be felt in the left lower quadrant. Carcinoma of the colon or diverticulitis was suspected. At operation pus escaped and a carcinoma of the jejunum, eight inches beyond the duodenojejunal flexure was found, which has perforated.

Perforations of Intestine Due to Swallowing of a Foreign Body—Perforations of the small intestine due to the swallowing of a foreign body are rare. Open safety pins frequently pass through the intestines of children without causing perforation. People at times wilfully swallow foreign bodies, others are swallowed unknowingly. Fish bones can cause trouble, and pelvic colon perforation from fish bones can occur, and cause peritonitis, but are not of frequent occurrence.

COLON PERFORATIONS—Perforation of the colon is as frequent in the female as in the male. The mortality is higher than in perforation of the stomach or duodenum, due to the greater infectiousness of the colonic content. Zimmerman,³⁸ Atwell,³⁹ and Allan⁴⁰ report cases of rupture of the colon by external violence. Titoner⁴¹ gives the history of a case in which the colon was completely separated from the rectum by external violence. Woodbury⁴² reports an instance in which a girl, age 14, fell seven or eight feet directly upon an erect stake. The tuberosity was first struck, and then the stake passed into the anus, up the rectum for two inches, through the rectal wall and then through the body in an oblique direction. Striking the ribs near the left nipple, it fractured three, and then made its exit. The stake was three inches in circumference. Twenty-seven inches of its length passed into the body, six or seven inches merging from the chest. The girl recovered so rapidly that she returned to school six weeks later.*

* Robert T. Morris⁴⁸ reported a case of compression perforation of the colon with five openings. He gathered all five openings around a central, large wick drain with catgut, and made no attempt at closure. The patient recovered.

Exclusive of violent injury, the three most frequent causes of perforation of the large intestine are diverticulitis, chronic ulcerative colitis and carcinoma. Bergen and Cox⁴³ have reported 50 cases in which perforation was caused by diverticulitis or carcinoma. Zengerling⁴⁴ cites the instance of an artificial perforation of the rectum following rectoscopy, and states that Menegaux, in 1933, collected ten cases of perforation of the rectum following rectoscopy. Five died. He, himself, reports the following case:

Case Report—Doctor Zengerling: The patient, a male, age 62, had a rectoscopy performed at 11 A.M., which was very painful. Shortly after midnight the patient was brought into the hospital with only slight pain. Roentgenologic findings indicated an injury to the intestines. Operation was performed 24 hours after the trauma. Loops of small intestine were located in the lesser pelvis, covered with a cloudy fluid. They were pushed forward and a large amount of fecal fluid escaped from the lesser pelvis, flowing from the ileocecal region toward the root of the mesentery. The rectum and culdesac had fibrinopurulent deposits. At the bottom of the culdesac there were two to three tablespoonfuls of purulent, brownish fluid. In the region of the pelvic colon, a rupture, 2 cm. long, was visible on the anterior aspect of the rectum to the left of the midline. The borders were not bleeding. Fecal matter was visible between them. After cleansing the lesser pelvis, the perforation was closed with two layers of sutures. An incision was made in the left flank and a sigmoidostomy established. The lesser pelvis was drained through a right stab wound. The intestine was opened with a thermocautery, intestinal flatus escaped. Four weeks later the sigmoidostomy was closed by operative procedure, and the patient made an uneventful recovery.

In our own series, there were 18 perforations of the colon. Of the 18 cases, 12 died (66.6 per cent). Twelve cases were perforations of diverticula of the sigmoid. Of the other six cases, there were four deaths. The average time of hospitalization was 55½ days. The average blood count was W.B.C., 14,800, 82 per cent polymorphonuclear leukocytes. The average temperature was 101.2° F., and the average pulse rate 100. Inflammation of the ascending colon, of unknown origin, caused one perforation. Perforation was caused by chronic ulcerative colitis in another case, and a tuberculous ulcer caused the perforation in a third case.

A huge retroperitoneal abscess, in one case, was caused by a perforation in the descending colon. This was incised and drained but the patient succumbed. At autopsy, a large perforation of the descending colon was found and in the microscopic sections of the colon typical amebae were present in the submucosa. This diagnosis had not been made during life, despite attempts to do so.

TABLE XXVII
RÉSUMÉ OF COLON PERFORATIONS

No. of Cases	Location	Cause	Operation	Result		
				Cured	Died	Autopsy
3	Ascending colon	Inflammatory?	1	1		
		Tuberculosis	1		1	
		Ulcerative colitis	1	1		
1	Descending colon	Amebic ulcer	1		1	1
12	Sigmoid colon	Diverticulitis	9	4	8	8
2	Recto-sigmoid	Ulcerative colitis	2		2	2
		Sepsis				
18			15	6	12	11
					66.6%	

There were two cases of perforation of the rectosigmoid. One was caused by ulcerative colitis with perforation and peritonitis, the other (discovered at autopsy) was in a case of sepsis following an infection with hemolytic *Streptococcus* after cholecystectomy and appendicectomy.

One of the inflammatory perforations of the ascending colon occurred in a child, age 5, and was so unusual that the case report is appended.

Case Report—A F, female, age 5, had had pain in the abdomen for four days, in the midumbilical region. A diagnosis of appendicitis was made. There was some rigidity of the right side of the abdomen and a definite, quite hard, tender mass could be felt one-half inch to the right of the umbilicus. At the time of the first operation, a large mass was found in the right lumbar gutter. It was irregular, and lay in the folds of the mesentery of the ascending colon, extending up to, and partly surrounding, the intestine just below the hepatic flexure and down to the ileocecal junction. There were many lymph nodes in the mesentery. The lumen of the ascending colon was encroached upon. An ileocolostomy was performed, with removal of two lymph nodes. Two weeks later an ileocecal resection was performed. The ascending colon and three inches of the transverse colon were removed together with a mass of lymph nodes. Pathologic diagnosis showed an acute suppurative colitis with perforation of the colon, and a chronic pericolitis with lymphadenitis and hyperplasia of the lymph nodes. The mucosa of the ascending colon was normal except for two small patches of congestion, about 6 Mm in diameter, and situated 2 to 4 cm above the ileocecal valve. The lower one showed an elliptical-mouthed perforation, 1 Mm in its greatest diameter, which led downward, at a 45° angle, and slightly to the right, into a mass of hemorrhagic, fibrous adhesions on the retroperitoneal surface, and was bound together with a mass of lymph nodes. No foreign body could be found.

Microscopic examination of serial sections of the colon, through the area of perforation, showed that the track was lined with a thick layer of fibrinous granulation tissue, covered in places with cylindric epithelium derived from the mucosa of the intestine. The granulation tissue extended for some distance beyond the tract and was infiltrated with many small round, plasma and endothelial cells. There was considerable destruction of the muscular coats and a generalized inflammatory cell infiltration of the intestinal wall. Sections through the congested area, in the vicinity of the perforation, showed a large irregular area of granulation tissue which had replaced the normal tissue of the submucosa, muscularis and serous coats. This tissue was very similar to that described above, being rich in small round, plasma and endothelial cells. Giant cells of foreign body type were occasionally encountered. The cause of perforation could not be determined from the sections examined.

Twenty-three years after resection, April, 1936, the patient was readmitted to Lenox Hill Hospital for a small papilloma of the abdominal wall. She was otherwise entirely well.

In our series, we had one case of perforation of the cecum, with the following history.

Case Report—W K, age 27, had had an appendicostomy for a severe ulcerative colitis, four months before readmission. Two and one-half hours after replacing a rubber catheter through the appendicostomy wound, he was seized with a severe abdominal pain on the right side. There was marked tenderness over this area and slight rigidity. An operation was advised on the chance that a perforation of the cecum might have occurred. The appendix was removed and a small perforation was discovered, two and one-half inches above the base of the appendix on the right side of the cecum, where one of the ulcers of the colitis had perforated. This perforation was sutured. It is now seven

months since this was done. The patient has gained 50 pounds in weight, and is markedly improved.

There were 12 cases of perforation of sigmoid diverticula, with eight deaths (66.6 per cent). All eight cases that died were autopsied.

Perforation of a diverticulum may be considered an emergency. We know of one case in which perforation occurred immediately upon the giving of a colonic irrigation to a patient with diverticulitis. A fecal concretion in a thin-walled diverticulum may perforate easily. The symptoms following perforation are very severe, but the preceding symptoms may have been vague and diagnosis missed.

The patients usually complain of malaise, constipation lasting weeks or even years. Then there is sudden pain in the lower abdomen which may be of 24 hours' to two weeks' duration, as in our series. Vomiting may be present. Abdominal distention, pain and tenderness are the outstanding physical signs. The blood counts in our series averaged W B C, 18,000, with 77 per cent polymorphonuclear leukocytes. The temperature and pulse averaged 102° F and 110, respectively.

Eggers⁴⁵ reported on a series of 24 cases of diverticulitis and sigmoiditis, which he had personally observed. Perforation took place in seven cases. In three, there was local abscess formation. In four, acute perforation took place into the free peritoneal cavity. One was drained early and recovered, another was treated expectantly for peritonitis, without knowledge at the time of the underlying cause, and finally recovered, while the other two died.

In five of our cases, roentgenograms were taken before operation. In one, the diagnosis of diverticulitis was made. In three, the condition was diagnosed as intestinal obstruction and in the fifth, as paralytic ileus. A preoperative diagnosis of probable diverticulitis or sigmoiditis was made seven times, intestinal obstruction once, acute appendicitis once, segmental enteritis once, and peritonitis of unknown origin once.

Operation was performed in nine of the 12 cases. Four were drained, of whom three died. The involved colon was exteriorized in three instances, with two deaths. Both cases in whom the appendix was removed and the peritoneal cavity drained recovered. In three cases, no operation was performed and the diagnosis was made at autopsy. The eight cases that died were all autopsied. Three showed evidences of sepsis and suppurative peritonitis, one, acute dilatation of the stomach (death on the fourth postoperative day), and in another, there were, in addition to perforation of the diverticulum with suppurative peritonitis, an hypernephroma, subphrenic abscess on the left with perforation of the diaphragm, suppurative pleurisy and a carcinoma of the right breast.

In three cases that were not operated upon, autopsy showed ruptured diverticula, mesenteric abscess, septic phlebitis and multiple liver abscess. In another case, generalized peritonitis with many diverticula filled with fecal material, and in a third, a ruptured diverticulum which had perforated into the mesentery and formed a retroperitoneal abscess.

The four cases which survived the perforation are herewith summarized

Case 1—A male, age 28, made a smooth recovery after removal of the appendix and simple drainage of the area where perforation had occurred in the sigmoid. There was a mass the size of a hen's egg. Perforation had occurred 24 hours previously.

Case 2—A female, age 50, had a history of 18 hours' perforation. The sigmoid was exteriorized and secondarily removed, the resulting colostomy was closed nine months later, with smooth recovery.

Case 3—A female, age 47. Roentgenologic examination, three years previously, showed a diverticulitis. A perforation occurred, with the slow development of an abscess between the bladder, uterus, and sigmoid. This was drained in 1937. To date, in spite of three attempts at excision of the fecal fistulous tract, we have not succeeded in closing it.



FIG. 6—Case 4. Roentgenogram, postoperative of perforation of sigmoid diverticulitis, showing presence of diverticula.

Case 4—A male, age 34, was operated upon in December, 1938. He had been ill for five days, with perforation occurring the day before admission. He was admitted with a temperature of 100.6°F. Shortly afterward, this rose to 103.8°F, W. B. C. 17,800, with 80 per cent polymorphonuclear leukocytes. The patient was operated upon with a preoperative diagnosis of segmental enteritis, pelvic peritonitis due to diverticulitis, or appendicitis.

An acute diverticulitis and pus in the pelvis were found. The appendix was removed and the pelvis drained. The patient made an uneventful convalescence, but still has a fecal fistula. Roentgenograms, taken after the operation, showed small diverticula, with an irregularly filled sigmoid (Fig. 6).

Perforations of the colon are always extremely serious surgical problems. The high degree of infectiousness of the colonic contents naturally creates a severe degree of peritonitis, unless nature has been kind enough to wall-off the diseased area sufficiently to prevent general peritonitis. Mortality is high. The more favorable results have been obtained in the younger patient, who is operated upon early and has better resistance.

SUMMARY AND CONCLUSIONS

(1) Perforations of the gastro-intestinal tract are classed as surgical emergencies or urgencies.

(2) Certain unusual cases of perforations of the gastro-intestinal tract, and important statistics, have been reported from the literature. These seem to be of special interest and value.

(3) The paper is based on a series of 151 cases of perforations of the gastro-intestinal tract, exclusive of perforations of the gallbladder and appendix, that were seen by the Surgical Services of the Lenox Hill Hospital, from 1923 to 1938.

(4) The total mortality of all cases, operated or not operated upon, was 42.3 per cent, indicating the seriousness of the condition.

(5) The majority of the cases were perforations of gastric and duodenal ulcers. Operative mortality ranged about 25 per cent. This is approximately the same mortality rate as that reported in other large series of cases.

(6) Perforations of gastric and duodenal ulcers can occur without any previous ulcer symptoms. This happens more frequently in gastric than in duodenal ulcers.

(7) The time element, between perforation of the ulcer and operation, is very important as to mortality. Apparently, perforations of duodenal are not as serious as those of gastric ulcers. In the cases that recovered the time element was approximately three times longer in the duodenal than in the gastric series.

(8) Primary, simple closure seems to give the best results, with lowest mortality.

(9) Secondary gastro-enterostomy after simple closure is rarely necessary. If pyloric stenosis develops, it usually occurs within one year of the primary closure, rarely later.

(10) Recurrent ulcer symptoms may be accompanied by hemorrhage. These recurrent ulcers are either gastric, duodenal or may be marginal if gastro-enterostomy has been performed. Gastric resection is occasionally required.

(11) Peritonitis with secondary pneumonia is the most frequent cause of operative mortality.

(12) Esophageal perforations are not frequent. They are attended with a high mortality. Early recognition in traumatic cases and early operation with extensive drainage are required to save the patient's life.

(13) Small intestine perforations are the result of a variety of etiologic factors, which are discussed and case reports given. Trauma is one of the most important causes. Shock may be immediate or delayed. If immediate, it should be treated first, followed by early operation. The surgical procedure should be as simple as possible.

(14) Perforations of the colon, sigmoid and rectum are accompanied by a very high mortality, due to the high degree of infectiousness of the colonic contents and resulting peritonitis. Perforation of sigmoid diverticula is the most common cause and mortality is high. Other causes of colon perforations are discussed and case reports given.

REFERENCES

- ¹ Gould and Pyle Anomalies and Curiosities of Medicine Saunders, 1897
- ² Guersant Bull de la Fac de Med de Paris, 73, 1812
- ³ Sigora, B Roentgenpraxis, 2, 140, February 1, 1930
- ⁴ Gross Lancet, London, 1, 249, 1885
- ⁵ Gamble, H ANNALS OF SURGERY, 107, 5, 701, May, 1938
- ⁶ Mackenzie, Sir M A Manual of Diseases of Nose and Throat London, 1884
- ⁷ Neue Jahrbucher der Deutschen Md u Chir, 1823
- ⁸ New Orleans Med and Surg Jour, 1853
- ⁹ Garcia Porvenir (El) Mexico, June 1854
- ¹⁰ Houston Dublin Hosp Rep, 5, 319, 1938
- ¹¹ Hinder Wchnschr f d Ges Heilk Berlin, 603, 1840
- ¹² Wunschheim Prager med Wchnschr, 18, No 3, 21
- ¹³ Collins Amer Therapeutist, New York, 1894
- ¹⁴ Lallemand Dictionaire des Sciences Med, 49, Paris, 1812
- ¹⁵ Eliason, E L, and Ebeling, W W Am Jour Surg, 24, 63-82, April, 1934
- ¹⁶ Guthrie, D N N Y State Jour Med, 23, 66, 1923
- ¹⁷ Mattingly, C W New Orleans Med and Surg Jour, 84, 18, 1931
- ¹⁸ Smith, F K Brit Med Jour 2, 1068, 1921
- ¹⁹ Searby, H Med Jour Australia, 17, 202, 1930
- ²⁰ Gilmour, J, and Saint, J H Brit Jour Surg, 20, 78, 1932
- ²¹ Woodall, Charles W Am Jour Surg, 35, 524, March, 1937
- ²² Harden, A S Jour Med Soc N J, 31, 400-401, July, 1934
- ²³ Butler, E Western Jour Surg, 42, 326-329, June, 1934
- ²⁴ Brenner, E C ANNALS OF SURGERY, 86, 393, 1927
- ²⁵ Graves, A M ANNALS OF SURGERY, 98, 197-209, August, 1933
- ²⁶ Shawan, H K ANNALS OF SURGERY, 98, 210-220, August, 1933
- ²⁷ Rhodes, G K, and Collins, D C California and West Med, 39, 173-177, September, 1933
- ²⁸ James, T G I, and Matheson, N M Lancet, 1, 945, May 5, 1934
- ²⁹ Black, J M Brit Med Jour, 2, 290-291, August 12, 1933
- ³⁰ Frost, J C, and Guy, C C Am Jour Surg, 37, 319, August, 1937
- ³¹ Gerster, J C A ANNALS OF SURGERY, 107, 783, May, 1938
- ³² Geill, C Quoted by Vance, B M Arch Surg, 16, 630-679, March, 1928
- ³³ Beekman, Fenwick ANNALS OF SURGERY, 90, 206, August, 1929
- ³⁴ Siegel, E Beitr z klin Chir, 21, 395, June, 1898
- ³⁵ Counsellor, Virgil, and McCormack, C ANNALS OF SURGERY, 102, 365, September, 1935
- ³⁶ Inlow, Wm Arch Surg, 21, 97, July, 1930
- ³⁷ Turner, P Proc Royal Soc Med, 1922-1923, 16, (Clim Sect 24), *ibid* 28, 181, December, 1934
- ³⁸ Zimmerman Wchnschr f d Ges Heilk, 603, 1840
- ³⁹ Atwell Indiana Jour Med, Indianapolis, 1875
- ⁴⁰ Allan Lancet, London, 2, 332, 1878
- ⁴¹ Titorier Jour de Med, Paris, 11, 1801-1817
- ⁴² Woodbury Nashville Jour Med and Surg, 14, 151, 1874
- ⁴³ Bargaen, J A, and Cox, F W Minn Med, 15, 466, July, 1932
- ⁴⁴ Zengerling, T Munchen med Wchnschr, 84, 1721, 1937
- ⁴⁵ Eggers, Carl ANNALS OF SURGERY, 94, 648, October, 1931
- ⁴⁶ Tilton, B J Am J of Surg, 32, No 2, 238, May, 1936
- ⁴⁷ McCreery, J A ANNALS OF SURGERY, 107, 350-358, March, 1938
- ⁴⁸ Morris, Robert T Personal communication
- ⁴⁹ Graham, Roscoe R Surg Gyn and Obst, 64, 235-238, 1937 *Ibid* 66, 269-287, 1938

SURGICAL ANASTOMOSES BETWEEN THE BILIARY AND INTESTINAL TRACTS OF CHILDREN*

FOLLOW-UP STUDIES

WILLIAM E LADD, M D

AND

ROBERT E GROSS, M D

BOSTON, MASS

FROM THE SURGICAL CLINIC OF THE CHILDREN'S HOSPITAL AND THE DEPARTMENT OF SURGERY,
HARVARD MEDICAL SCHOOL, BOSTON, MASS

ON THREE previous occasions^{2, 4, 5} we have published reports on the surgical treatment of congenital atresia of the bile ducts and of congenital dilatation of the common duct. The obstruction in some of these patients can be relieved by joining various parts of the biliary tract with the stomach or duodenum. The early results in such cases have been very satisfying, but no significant observations on the end-results have ever been recorded. It is the purpose of this communication to summarize the late findings in all patients with a congenital abnormality of the bile passages which we have treated by surgically joining biliary and intestinal systems.

The Material Available for Study—In 1916, Holmes³ called attention to the possibility that many infants with congenital atresia of the hepatic or common duct might be cured if surgical measures were instituted for uniting these small obstructed ducts with the alimentary tract. Since that time we have explored almost all infants who have entered the Children's Hospital with such malformations. One of us (W E L), in 1927, performed the first successful operation for relief of congenital atresia of the bile ducts. To date, 45 babies with biliary atresia have been operated upon in this hospital (Fig 1). Nine of these were found to be operable, and in eight patients a blind hepatic duct, a blind common duct, or the gallbladder was anastomosed with the stomach or duodenum. Three of these babies died shortly after operation, one expiring on the second day of hemorrhage, one on the ninth day of peritonitis, and one at the end of three months from perforation of the duodenum by an inlying tube which led to a fatal peritonitis. Of the entire group, then, five have survived.

Approximately 130 cases of congenital cystic dilatation of the common bile duct—occurring in children and adults—have been recorded in the literature. In 1933, Gross² reviewed 52 of these which had been observed in the childhood group. To date, we have personally encountered six children with this condition, five of whom were treated by drainage of the biliary tract into the stomach or duodenum (Fig 2).

* This publication was aided by a grant from the Godfrey M Hyams Trust
Submitted for publication February 14, 1940

Combining the above two groups, there are now available for study ten patients in whom there has been a surgical anastomosis between the biliary and intestinal systems

Types of Operation—Congenital obliteration of the bile ducts usually involves the entire extrahepatic system so that there is no means for escape of bile from the liver. In rare instances, a complete obstruction may appear at

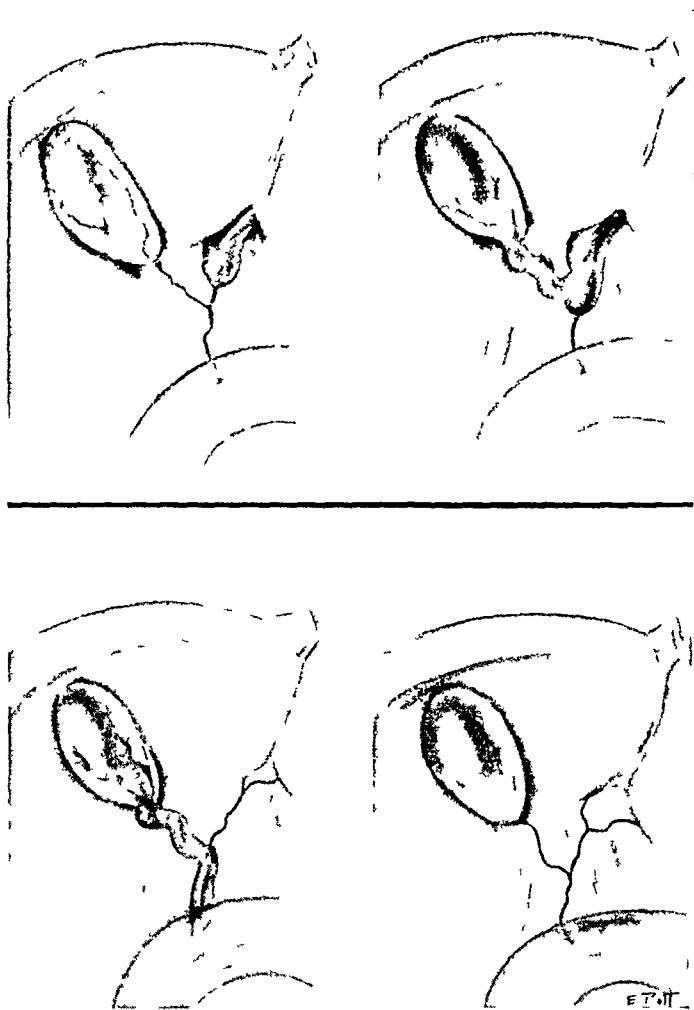


FIG. 1—Types of atresia of the extrahepatic system found in 45 cases which were surgically explored. *Above* Types of cases which are operable by joining the blind hepatic or common duct to the duodenum. *Below* Types of cases which are inoperable and no relief of jaundice can be instituted.

the lower end of the hepatic duct, and the ductal system is normal above this. In a slightly higher percentage of cases, an atresia is found in the common duct, and the system is patent above this. The types of these anomalies, as observed in our 45 cases, are indicated in Figure 1. Case 2 had an atresia of the hepatic duct and was treated by hepaticoduodenostomy. Cases 1, 3, 4 and 5 all had a complete obstruction of the common duct, and were treated by performing a choledochoduodenostomy or a cholecystoduodenostomy.

In the above cases, when the hepatic or common duct was joined to the

intestine, the technic employed was as follows. The blind duct was carefully opened and a short piece of small (Nos 8 or 10 F) urethral catheter was pushed up into it. A small opening was then made in the duodenal wall, and the lower end of the catheter and the duct were threaded down into the duodenum. The duct was then joined to the intestinal wall with a single circumventing row of interrupted silk sutures which were so placed that the end of the hepatic (or common) duct pierced the intestinal wall. In this way the mucous membrane of the duct was placed in close apposition to the duodenal mucosa and the anastomosis had been completed over the short piece of rubber tubing. If the rubber tube was short (one-half to three-fourths or an inch), it always spontaneously passed later into the intestine and was discharged in the stool. With this technic, a nice approximation of



FIG 2—Drawing showing congenital cystic dilatation of the common bile duct. The dilatation is due to either a stenosis at the lower end of the duct or else to an achalasia which prevents proper function of the sphincter of Oddi. Surgical treatment consists of joining the gallbladder to the intestine, or preferably, anastomosing the common duct to the duodenum.

duct and intestine could be accomplished and there was assurance that an adequate lumen was established at the anastomotic site.

Five individuals with cystic dilatation of the common duct were treated in three different ways. In two, a choledochoduodenostomy was established, in two, the gallbladder was joined to the duodenum, while in one case, a cholecystogastrostomy was performed. In one of the cholecystoduodenostomies the anastomosis was made with the aid of a Murphy button, but all of the other four anastomoses were performed by a careful suture of the common duct (or gallbladder) to the stomach or duodenum. The suture in these four cases was always done with an external row of continuous silk or fine chromic catgut and an inner layer of fine, plain catgut to act as a hemostatic stitch and to approximate the mucosal edges accurately. Of the three forms of operation for choledochal cysts—cholecystogastrostomy, cholecystoduodenostomy, and choledochoduodenostomy—we have now come to believe that the last procedure is the one of choice.

Results of Operations—As mentioned above, there were three mortalities occurring soon after operation. These were the first three cases which were found to be operable (in the atresia group) and we regard the deaths as attributable to technical errors which should not be committed to-day with our improved methods of operation. The ten cases which ultimately survived anastomosis between the biliary and alimentary systems have all been reviewed with the purpose of determining what is the end-result to date concerning (1) The function of the alimentary system (2) The possible danger of ascending cholangitis (3) The condition of the liver which was previously known to have an extensive obstructive cirrhosis (4) The general development and health of the patient. These ten patients have all been interviewed in 1940 and their present condition evaluated. These ten patients are, therefore, reviewed at 19, 16, 14, 13, 11, 8, 6, 6, 5 and 5 years after operation (Table I).

The findings in these ten patients may now be summarized under the following headings:

(1) *The Function of the Alimentary System*—In every case, there is clinical evidence that the alimentary system is functioning normally. By this is meant that there is no indigestion, that fatty foods are well tolerated, that the stools are normally colored, and show nothing to suggest faulty absorption of fat.

(2) *The Possible Dangers of Ascending Cholangitis*—In Case 7, there is, obviously, a chronic, recurring infection of the biliary tract. This patient was operated upon in 1924 for a choledochal cyst, and a cholecystoduodenostomy was performed with a Murphy button. We assume that the hole which was made at the anastomotic site by this method was too large, for this is the only case in the series which shows evidence of cholangitis. While it must be admitted that this patient does have recurring cholangitis, she has had only mild incapacitation and is at present a senior student in college. In the other nine patients jaundice disappeared within a few weeks after operation and has never recurred since then. In none of these nine patients has there been fever, upper abdominal pain, or chills which could not be readily explained on some other basis.

(3) *Condition of the Previously Cirrhotic Liver*—It has been claimed by some authors that there is little use in effecting a surgical repair for atresia of the bile ducts, because the individual will subsequently die of hepatic insufficiency. It was the contention of these writers that the advanced cirrhosis which is always found in such babies would eventually lead to liver atrophy and failure. We have never seen any evidence of such a series of events, and in no case has ascites occurred. The only evidence of possible portal obstruction is in Case 2, a boy, age 7, in whom the tip of the spleen is just palpable, in all other cases, the spleen cannot be felt. In Case 7, the liver is slightly enlarged, but in all the other patients the liver edge can just

be felt at the costal margin and appears neither enlarged nor atrophied. It is, therefore, evident that these children possess extraordinary powers of regenerating liver substance and that the presence of cirrhosis is not a contraindication to surgical procedures if an operable condition is found in the biliary ductal system.

TABLE I
SUMMARY OF TEN PATIENTS WITH SURGICAL ANASTOMOSES BETWEEN THE BILIARY SYSTEM AND INTESTINAL TRACT

CASES WITH ATRESIA OF THE EXTRABILIARY SYSTEM							
Case No	Hosp No	Sex	Age at Operation	Pathologic Condition	Year of Oper	Type of Operation	Results in 1940
1	103,192	F	4 mos	Atresia of common duct	1927	Choledochoduodenostomy	Excellent No biliary symptoms
2	160,956	M	2 mos	Atresia of hepatic and common ducts	1932	Hepaticoduodenostomy	Excellent No biliary symptoms
3	181,052	M	1 mo	Atresia of common duct	1934	Choledochoduodenostomy	Excellent No biliary symptoms
4	187,764	M	2 mos	Atresia of common duct	1934	Choledochoduodenostomy	Excellent No biliary symptoms
5	193,956	F	1 mo	Atresia of common duct	1935	Cholecystoduodenostomy	Excellent No biliary symptoms
CASES WITH CONGENITAL DILATATION OF THE COMMON BILE DUCT							
6	44,292	F	3 mos	Idiopathic dilatation of common duct	1921	Cholecystogastrostomy	Excellent No biliary symptoms
7	77,249	F	5 yrs	Idiopathic dilatation of common duct	1924	Cholecystoduodenostomy (with Murphy button)	Alive and active, but has recurring jaundice
8	91,602	F	5 yrs	Idiopathic dilatation of common duct	1926	Cholecystoduodenostomy	Excellent Occasional abdominal pain but no biliary symptoms
9	119,770	F	5 yrs	Idiopathic dilatation of common duct	1929	Choledochoduodenostomy	Excellent No biliary symptoms
10	179,425	F	2 yrs	Idiopathic dilatation of common duct	1934	Choledochoduodenostomy	Excellent No biliary symptoms

(4) *The General Development of the Individuals*—In every case of this series the individual has had a normal physical development, has been

attending school, and has been engaged in extracurricular activities. Case 2 is a little underweight for his age, but his mother states that all of her children have been small. It was surprising, and satisfying, to see again the older members of the series, for they are all robust, ruddy in appearance, well-developed, and well-nourished. Some impression of the general condition of these patients can be gained from the photographs accompanying the case reports, all of which were taken in 1940.

(5) *The Appearance of a "Hepatorenal" Syndrome*—In passing, it is of some interest to note that no case in this series showed the slightest clinical evidence of uremia, oliguria, circulatory collapse, or death after the sudden release of dammed-up bile from the biliary passages. If the proponents of the theories regarding "liver deaths" are correct, the cases in this series should provide excellent material for the development of this syndrome. The infants with ductal atresia have had complete obstruction of the biliary passages for several months, and have had icteric indices as high as 200, and yet none of them has developed a "hepatorenal" syndrome after operation.

(6) *Abnormalities in Function of the Gastro-Intestinal Tract*—The union of bile ducts or gallbladder with the stomach or duodenum naturally causes some distortion of the gastric antrum, the pylorus or duodenum. This, however, has not given rise to any symptoms of anorexia, postprandial distress, nausea or vomiting. Roentgenologic examination of several of these patients, with the aid of a barium meal, has shown dislocation or angulation of the alimentary tract in the region of the anastomosis, but there has been no impediment to the passage of barium beyond this point. In none of these cases which were thus studied could we find regurgitation of barium into the biliary passages.

CASE SUMMARIES

Case 1—R. L. was a four-month-old female infant who entered the hospital, March 22, 1927. There had been onset of jaundice at two weeks of age. This had been persistent and had gradually increased in intensity. The stools had been white since birth. There had been occasional vomiting. There was failure to gain weight normally.

Physical Examination showed a well-developed, poorly nourished infant with deep jaundice. The spleen was palpable and the liver was obviously greatly enlarged. The stools were white, and the urine showed a strongly positive test for bile pigments.

Operation—Drop ether anesthesia. The liver was greatly enlarged and was deep green in color. The gallbladder was greatly distended and on opening it there was a gush of bile. The common duct was found to end blindly a few millimeters below the point where the hepatic and cystic ducts joined. Choledochoduodenostomy was performed. The blind common duct was opened and a small rubber catheter was threaded down through the gallbladder, cystic duct, and the patent portion of the common duct. Clamps were now placed across the duodenum, in order to prevent subsequent soiling of the field. A small opening was made in the duodenum, the catheter was threaded down into the duodenum, and the common duct was joined to this part of the intestine with interrupted silk mattress sutures. This was done in such a way that the common duct extended through the wall of the duodenum.

Postoperative Course—The rubber tube was left in place for several days, the jaundice rapidly cleared, and the stools became brown colored. The baby was discharged.

home in satisfactory condition on the twenty-third postoperative day. She has been followed intermittently since that time. The general health has been excellent. She has developed normally and has been active in school athletics. At no time since operation has she had symptoms referable to the biliary system. There has been no jaundice, unexplained fever, or abdominal swelling (ascites). When last seen in January, 1940, at the age of 13 she was well-developed and well-nourished; there was no jaundice, and the liver edge could be just felt at the costal margin. The spleen was not palpable (Fig. 3).

Case 2—J. M. was a two-month-old male child who entered the hospital, June 14, 1932. At birth the baby was definitely jaundiced. This condition persisted and increased in intensity. Since birth the stools had always been white in color, and the urine had always stained the diaper a deep yellow. On several occasions there had been mild episodes of vomiting. At no time did the vomitus contain bile.

Physical Examination—Externally the baby appeared to be well-developed and rather poorly nourished. The skin and mucous membranes were deeply icteric. The abdomen was distended; the increased size was mostly due to a greatly enlarged liver which extended well down below the umbilicus. The spleen was not palpable. The stools were white and the urine showed a strongly positive test for bile pigments. Icteric index was 150.

Operation—Drop ether anesthesia. The liver was found to be markedly cyanotic and a deep green color. The gallbladder was extremely small and buried very deep in the sulcus of the liver. When opened this contained only a few drops of clear, colorless mucoid material. An extensive search in the gastrohepatic ligament showed the common and cystic ducts to be represented by only a small cord of fibrous tissue. Just at the border of the liver was a small nubbins 5 or 6 mm. in diameter, which was the blind end of the hepatic duct. This was anastomosed to the duodenum over a small piece of No. 8 F soft rubber urethral catheter. This was effected by inserting two mattress sutures of arterial silk to join the blind duct and the duodenum, then opening the duct and the duodenum inserting one end of the catheter into the hepatic duct and the other into the duodenum and then interiorly inserting several mattress sutures, leaving the catheter in place.

Postoperative Course—The baby ran a stormy course for several days. There were repeated hemorrhages in several parts of the body, which were brought under control with transfusions. The piece of rubber tubing was spontaneously passed in the stool. By the end of three weeks the jaundice had disappeared. The child was discharged six weeks after operation. The boy has been seen from time to time since operation, and his general condition has been quite satisfactory. He has always been slightly underweight, but his mother states that all of her children have been small. He has been active and attends school. Since operation there has never been jaundice, unexplained fever, abdominal pain, or intolerance to fatty foods. Examination, in January, 1940, showed him to be slightly underweight but otherwise in good health. The child was jovial. The liver edge could be felt about 1 cm. below the right costal margin from the xiphoid process to the midnipple line, but the liver could not be felt below the costal border laterally. The tip of the spleen was just palpable. There was no jaundice (Fig. 4).

Case 3—G. K. was a 17-day-old male infant who entered the hospital April 28, 1934 because of jaundice since birth. The stools had always been soft and grayish-white in color. He had never vomited.

Physical Examination showed a small baby (five pounds, 12 ounces) who was deeply jaundiced. The liver was greatly enlarged to palpation and there was some shifting fluid within the abdominal cavity. The stool was white, and the urine was deeply bile stained. The icteric index was 200.

Operation—At seven weeks of age an exploratory celiotomy was performed. The liver was greatly enlarged, deep green in color, and markedly cyanotic. The gallbladder was tensely filled with green bile. The common duct ended blindly 5 or 6 mm. below

the junction of the hepatic and cystic ducts. Below this there was only a thread of fibrous tissue running downward toward the duodenum. A choledochoduodenostomy was established, the anastomosis was effected over a short piece of rubber catheter, which was left in place. The common duct was sutured to the duodenal wall with interrupted mattress stitches of silk.

Postoperative Course—The patient had a very satisfactory postoperative course. Jaundice gradually cleared and completely disappeared in about one month's time. After three weeks, the weight began to increase. Six days after operation bile first appeared in the stools, and after this the stools were normally colored. The small piece of rubber tubing was passed per rectum on the ninth postoperative day. The infant was discharged home in good general physical condition on the forty-second postoperative day. The patient has subsequently moved to a distant part of the country but a letter from the mother, in January, 1940, states that he is "a lovely healthy boy full of vigor and fun, and so far as I know perfectly healthy. He has rosy cheeks, is good and strong, and is a muscular child."

Case 4—B. H. was a nine-week-old male infant who entered the hospital, December 2, 1934. He had been jaundiced for three weeks. The stools had always been clay-colored and the urine gradually developed an amber color.

Physical Examination showed the baby to weigh seven pounds, 11 ounces, and to be somewhat undernourished. There was only a small amount of subcutaneous fat. There was a deep jaundice. The abdomen was protuberant and there was some dilatation of veins over the abdominal wall and lower chest. The edge of the liver protruded downward almost to the umbilicus. The tip of the spleen could be easily felt. The stool was white, and the urine had a strongly positive test for bile. The icteric index was 100.

Operation—The liver was deep green, was markedly cirrhotic, and had an increased firmness. The gallbladder was not enlarged, but did contain green bile. The common duct ended blindly just above its junction with the duodenal wall. The common duct above this was only 4 or 5 mm in diameter. A hole was made in the duodenum, and a small piece of catheter was passed upward into the opening common duct and also downward into the duodenum. An anastomosis was made over this piece of catheter. Sutures of arterial silk were employed for the anastomosis.

Postoperative Course—The patient ran a low febrile course for some days. On the sixth postoperative day the piece of rubber catheter was passed per rectum. Thereafter, the stools became at first green and then brown in color. The jaundice cleared rapidly, and the icteric index had dropped to 10 by the end of the first month. It was almost one month before the clinical evidence of jaundice had disappeared. The baby was discharged on the thirty-ninth postoperative day. The child was last examined in January, 1940. At that time there was no jaundice or other abnormality. The weight gain had been good and the child was in excellent general health.

Case 5—B. A. J. was a six-week-old infant who entered the hospital, July 18, 1935. Jaundice was first noted on the fourth day of life. This had gradually increased in severity. No note was made concerning the character of the stools. The baby was primarily brought to the hospital because of hemorrhage from the umbilicus.

Physical Examination—The patient was intensely jaundiced, and was in a critical condition because of hemorrhage from the navel. Temperature 95° F, pulse 200, and respirations very irregular. Immediate transfusion improved the patient's condition, and the hemorrhage promptly ceased. The tip of the spleen could be felt and the liver was noticeably enlarged. The stool was white, the urine was deeply pigmented, and the icteric index was 75.

Operation—The liver was moderately enlarged, definitely cirrhotic, and had a deep green color. The hepatic and cystic ducts appeared to be normal and the gallbladder was greatly distended with green bile. No common duct could be found. A cholecystoduodenostomy was performed. This was effected with two layers of fine plain catgut, reinforced with a few interrupted sutures.

Postoperative Course—In a few days the stools became green and subsequently had a brownish color. There was considerable diarrhea for two weeks, which subsequently disappeared. After a long, stormy course the infant finally began to take her formula fairly well and to gain a little weight. Jaundice cleared slowly. Because of protracted diarrhea and difficulties of feeding, hospitalization was continued for three months. Since that time the general condition has been excellent. The patient has been entirely asymptomatic. She has had no jaundice, unexplained fever, abdominal pain, abdominal swelling, or other symptoms suggesting biliary insufficiency or disease. When last examined, in January 1940, she was active and somewhat slender. Weight 37 pounds. There was no jaundice. The liver edge could be barely felt just below the xiphoid, but

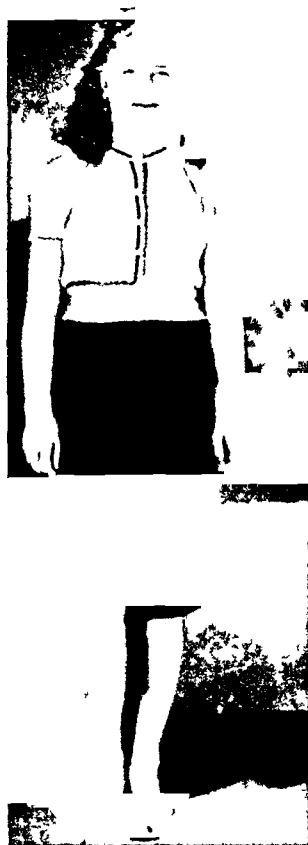


FIG 3



FIG 4

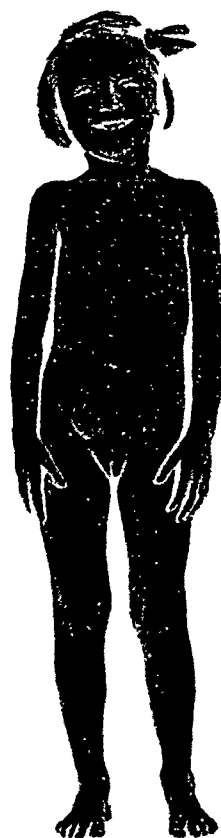


FIG 5

FIG 3—Case 1. Photograph of 13 year old girl, 13 years after choledochoduodenostomy for atresia of the common duct. General health is excellent. There have been no symptoms of cholangitis or hepatic insufficiency.

FIG 4—Case 2. Photograph of eight year old boy, eight years after hepaticoduodenostomy for atresia in the lower end of the hepatic duct. The child is slightly underweight but is otherwise in good health.

FIG 5—Case 5. Photograph of five year old girl, five years after establishment of a cholecystoduodenostomy for atresia of the common duct. There has been no evidence of biliary infection at any time.

the spleen was not palpable (Fig 5). Roentgenologic examination, with the aid of a barium meal, showed the pyloric end of the stomach and the duodenum to be further toward the right than usual. There was no obstruction to the passage of barium. No barium could be seen regurgitating into the gallbladder.

Case 6—M. E. was a three-month-old female infant who entered the hospital, November 29, 1921. During the first week of life, she occasionally vomited. At two weeks of age jaundice was first noted. The stools were normally colored for the first four or five days, but after that they became acholic.

Physical Examination showed the child to be poorly nourished and rather thin. There was a deep yellowish-green discoloration of the skin, sclerae and mucous membranes.

The liver edge was palpable about 1 cm below the costal margin. The tip of the spleen was barely felt.

Operation—The liver showed definite but slight cirrhosis, the gallbladder was distended, and the common duct was greatly dilated. The common duct was not opened for examination of the passageway through the ampulla of Vater. However, it was assumed that a small opening into the duodenum must have existed because of the definite presence of bile in the stools during the first four or five days of life. A cholecystogastrostomy was established, with the gallbladder turned over onto the anterior surface of the stomach. An outer row of fine silk, continuous sutures was reinforced internally with a row of plain continuous catgut.



FIG 6



FIG 7

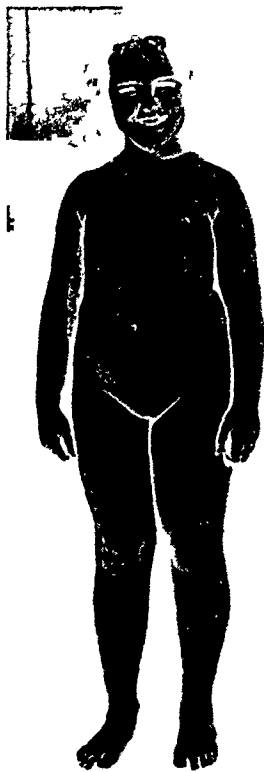


FIG 8

FIG 6—Case 6. Photograph of 19 year old girl, 19 years after establishment of a cholecystogastrostomy for idiopathic dilatation of the common bile duct. Patient's weight is 128 pounds and health is excellent. No cholangitis has ever appeared.

FIG 7—Case 8. Photograph of 19 year old girl, 14 years after cholecystoduodenostomy for cystic dilatation of the common duct. Health excellent. Weight 130 pounds. No jaundice.

FIG 8—Case 10. Photograph of eight year old girl, six years after choledochoduodenostomy for congenital cystic dilatation of the common duct. General health is excellent. There is no evidence of hepatitis, jaundice, or other abnormality.

Postoperative Course—Following operation, the child's condition was very precarious. Stimulants and parenteral fluids were necessary to improve her circulation. After the first week her general condition gradually improved and jaundice was beginning to disappear. Bile pigments appeared in the stools. At the time of discharge, on the fifty-sixth post-operative day, the urine and stools were normal and the jaundice had completely disappeared.

Roentgenologic examination of the gastro-intestinal tract, ten years after operation, showed the duodenum to be displaced upward and more to the right than normal. However, there was no obstruction at the outlet of the stomach. There was no reflux of barium into the gallbladder. This patient has been perfectly well throughout her entire

life since hospital discharge. At no time have there been gastro-intestinal symptoms, vomiting, jaundice, indigestion, unexplained fever, or clay-colored stools. Apparently, the release of bile into the stomach has not produced any disturbance of digestion at any time. When last examined in January, 1940, she was in excellent physical condition, was very stocky, well-nourished, and possessed a good sense of humor. There was no jaundice. Interestingly enough, the scar of the abdominal incision, which was two inches long at the time of operation, had grown with the individual and was now five inches in length. The liver edge could not be felt below the costal margin. The spleen was not palpable. There was no evidence of intraperitoneal fluid. Weight 128 pounds (Fig. 6).

Case 7—E. S. was a five-year-old girl who entered the hospital, December 8, 1924. At recurring intervals since birth the child had been jaundiced. Between these periods the skin color was almost normal but jaundice had never fully disappeared. During the past four months there had been intermittent upper abdominal pain and vomiting.

Physical Examination—The girl was well-developed and well-nourished, but there was a marked jaundice. Liver edge could be felt 3 cm. below the costal margin. An icteric index was not recorded but there were frequent subsequent notes stating that the child was deeply jaundiced.

Operation—The liver was somewhat enlarged, was slightly cirrhotic, and was bile stained. The gallbladder was greatly distended. The common duct was greatly enlarged but bile could be expressed into the duodenum. This cystic dilatation of the common duct was treated by establishing a cholecystoduodenostomy with the aid of a Murphy button.

Postoperative Course—Within one week it was noted that the jaundice was disappearing. The stools were consistently normal in color after the first week. The Murphy button was never identified in a stool, but roentgenologic examination on the fifteenth postoperative day showed it to have disappeared from the abdomen. At the time of hospital discharge, on the twenty-third postoperative day, jaundice had entirely vanished.

Subsequent Course—This patient has had recurring troubles. She was free of jaundice for some months after discharge from the hospital, but then began to have recurring attacks of what is apparently an ascending cholangitis. Jaundice is present most of the time. At some periods it is hardly noticeable while at other times it is quite marked. There are episodes of moderate upper abdominal pain associated with some fever, which incapacitate the individual for several days during the height of an attack. Her general development, however, has been good. When last heard of, in January, 1940, she was able to carry on activities as a senior student in college. Inasmuch as this is the only unsatisfactory result in the entire series herewith presented, we are led to believe that the establishment of a cholecystoduodenostomy with the aid of a Murphy button was a poor technical procedure. Apparently the communication which was thus established made too large an opening, so that the duodenal contents readily regurgitated into the gallbladder and biliary passages. We are, therefore, led to believe that anastomoses between the biliary and intestinal tracts should be performed by a careful suture of the apposed hollow visci, care being taken that the opening is not too small and yet is not so large that gastro-intestinal contents can escape into the biliary tract.

Case 8—E. H. was a five-year-old girl who entered the hospital, March 11, 1926, complaining of intermittent attacks of abdominal pain and vomiting since infancy. With each attack there had been a definite yellowish discoloration of the skin.

Physical Examination showed a well-developed, very well-nourished child who was having no discomfort at the time. The skin was markedly icteric. In the right upper quadrant of the abdomen there was a rather firm, smoothly rounded, nontender mass which did not appreciably move during inspiration. Above this the edge of the liver could be just felt below the costal margin. The stool at this time was clay-colored.

Operation—When the abdomen was opened, the mass was found to be an enormously dilated common duct, which was about the size of an orange. On draining the gallbladder with a trochar and cannula, the distended common duct collapsed. It was decided

to perform a cholecystoduodenostomy. The anastomosis was made with the use of an outer layer of fine plain catgut and an inner continuous layer of plain catgut, which approximated the mucosal edges.

Postoperative Course—Following operation the child did extremely well. Jaundice completely disappeared, there was no recurrence of abdominal pain or vomiting. She was discharged on the fourteenth day. A gastro-intestinal barium series, in April, 1928, showed no apparent duodenal stasis or deformity. No barium could be seen regurgitating into the gallbladder. This girl has been seen on many occasions for follow-up studies. Her general health has been excellent. She has graduated from high school. At no time since hospital discharge has there been jaundice, clay-colored stool, or unexplained fever. On a few occasions she has had mild attacks of abdominal pain, the localization of which is not certain. These are usually related to constipation, and with proper evacuation the pain completely disappears. Examination, in January, 1940, shows this patient to be very sturdy, well-developed, quite muscular and in excellent general health. There is no jaundice. The liver edge cannot be felt below the costal margin. Weight 130 pounds (Fig 7).

Case 9—M. H. was a five-year-old girl who entered the hospital April 6, 1929. At four years of age there had been an episode which had been diagnosed as catarrhal jaundice. Since then there had been recurring attacks during which the child was jaundiced, the stools were light in color, and the upper abdomen was distended. During the last few attacks there had been abdominal pain.

Physical Examination—The girl was poorly nourished and moderately jaundiced. The upper abdomen was enlarged and a bulging nontender mass could be felt below the costal margin. The stool was light in color but contained traces of bile. Icteric index 40.

Operation—The gallbladder was distended and was pushed forward, but a mass, the size of a grapefruit, lay behind it and toward the midline. This large mass was obviously an enormously distended common duct. A choledochoduodenostomy was established, with the use of a double row of sutures. The first, of silk, included only serosal layers, but the second, of catgut, joined the mucosal surfaces.

Postoperative Course—The jaundice cleared very rapidly, and the stools returned to normal color. Subsequent examinations showed no palpable mass in the right upper quadrant. She was discharged on the thirteenth postoperative day. A gastro-intestinal series, on the twelfth postoperative day, showed some distortion of the duodenum, but no evidence of the anastomosis between the biliary tract and duodenum. This child has subsequently moved to another community, but a follow-up letter shows that she has had a satisfactory postoperative course. At no time has there been jaundice or evidence of cholangitis.

Case 10—B. N. was a two-year-old girl who entered the hospital, March 9, 1934. She had been jaundiced for five weeks and the stools had become gray.

Physical Examination—The child was deeply jaundiced. The liver was considerably enlarged, and there was a tense mass in the right upper quadrant of the abdomen which was palpable below the liver. Temperature 101° F. The stools were clay-colored, the urine contained bile, and the icteric index was 35.

Operation—The liver had an increased consistency but did not appear to be cirrhotic. The gallbladder and cystic duct were not enlarged. The common duct was dilated to a lemon-sized cystic structure. Anastomosis was made between this dilated common duct and the second portion of the duodenum, using a double layer of catgut. The stoma was 7 or 8 mm in diameter.

Postoperative Course—The child's condition gradually improved, jaundice completely disappeared, and no mass could be felt in the right upper quadrant postoperatively. She was discharged home on the twentieth postoperative day. This patient has done extremely well. At no time has she had abdominal complaints since hospital discharge. There has been no jaundice, unexplained fever, abdominal pain, or indigestion. Fatty foods are well tolerated. Examination, in January, 1940, shows her to be extremely well-nourished and

slightly obese. She is very jovial. The liver edge cannot be felt below the costal margin. No mass or thickening can be made out in the right upper quadrant (Fig. 8).

SUMMARY—Follow-up notes are presented on ten patients who had anastomoses between the biliary and alimentary systems for treatment of either atresia of the bile ducts or idiopathic dilatation of the common bile duct. The condition of these patients has been reevaluated five to 19 years after the operative procedures. One individual has had recurring cholangitis, but the cholecystoduodenostomy in this case was performed with a Murphy button. In the other nine patients, the hepatic duct, common duct, or gallbladder was carefully anastomosed to the stomach and duodenum, and none of these nine has had cholangitis at any time. The livers in these individuals all showed marked obstructive cirrhosis at the time of operation, but none has shown any hepatic insufficiency since operation. It, therefore, appears that the liver has remarkable powers of regeneration under these circumstances, and that this repair can take place without subsequent portal obstruction.

CONCLUSIONS

A study of this material leads us to believe that it is not necessary to attempt prevention of ascending biliary infection by inserting biliary ducts into the intestine in an oblique or valve-like fashion. Nor is it essential to insert a bile duct into a clean side-arm of intestine to prevent soiling of the biliary passages. At least these statements hold true for patients in the childhood group. We are convinced that successful issue in these cases depends upon the care with which the anastomosis is performed. The operative procedure must be performed so that mucous membrane of the bile duct or gallbladder is accurately apposed to the mucosa of the stomach or duodenum, and no stenosis must exist at the anastomotic site. Under these conditions the long-time follow-up results of anastomoses between biliary and alimentary tract have shown very satisfactory results in our hands.

REFERENCES

- ¹ Blocker, T. G., Williams, H., and Williams, J. E. Traumatic Rupture of a Congenital Cyst of the Choledochus. *Arch Surg*, 34, 695, 1937.
- ² Gross, R. E. Idiopathic Dilatation of the Common Bile Duct in Children. *Jour. Pediat.*, 3, 730, 1933.
- ³ Holmes, J. B. Congenital Obliteration of the Bile Ducts. Diagnosis and Suggestions for Treatment. *Am Jour Dis Child*, 11, 405, 1916.
- ⁴ Ladd, W. E. Congenital Atresia and Stenosis of the Bile Ducts. *J A M A*, 91, 1082, 1928.
- ⁵ Ladd, W. E. Congenital Obstruction of the Bile Ducts. *ANNALS OF SURGERY*, 102, 242, 1935.

EXPLORATION OF THE COMMON BILE DUCT*

FRANK GLENN, M D

NEW YORK, N Y

FROM THE DEPARTMENT OF SURGERY OF THE NEW YORK HOSPITAL AND CORNELL UNIVERSITY MEDICAL COLLEGE
NEW YORK, N Y

SOME MONTHS AGO, the writer reviewed the Proceedings of the New York Surgical Society since its organization, in search of the first comment on exploration of the common duct to be presented before it. It was found that, on March 11, 1891, Dr Charles McBurney¹ had read a short paper about a patient operated upon by him for stone in the common bile duct. The patient had been ill with jaundice for a long time and had lost 63 pounds in weight. The common duct was approached through an incision in the duodenum, the ampulla of Vater divided and the common duct split to remove the stone. The patient recovered and regained her health.

In October of the following year, Dr Robert Abbe² read a paper before this Surgical Society entitled "Cases of Gallbladder Surgery." In it he advocated the removal of the gallbladder for cholelithiasis, incision of the common duct and removal of stones in choledocholithiasis, followed by repair of the defect in the duct with fine silk sutures and drainage of the common duct by means of a rubber tube. He also drained the operative field. The four cases he presented were considered to be progressing toward a fatal outcome because of the complete obstruction of the common duct. In reviewing the literature, he credited Crede, Lawson-Tait, Kummell, Senger and Gregg Smith with voluminous articles on this subject.

Since his time, articles on the surgery of the biliary tract have increased year by year until now it is almost beyond the capacity of any one man to read them carefully, as they appear. It is not my purpose to review this extensive literature. I wish, rather, to report briefly our experience with exploration of the common duct over a period of six years at the New York Hospital. Some of our patients exhibited the common problems encountered in surgery of the biliary tract, such as the elusive stone, stenosis of the common duct and excessive bleeding due to jaundice. Every surgeon and clinic interested in this field of surgery deals with these problems in their own way. I shall review our cases and describe some simple methods which we have adopted in handling them.

From September 1, 1932, to September 1, 1938, 907 patients were subjected to operation for nonmalignant disease of the gallbladder and biliary tract. One hundred twelve of these (12.1 per cent) were explored for obstruction of the common duct (Table I). The common duct was routinely opened and searched for obstruction in all cases (a) in which there were stones palpable

* Read before the New York Surgical Society, May 10, 1939. Submitted for publication April 7, 1939.

in the duct, (b) in which there was a history of progressive jaundice or repeated attacks of jaundice, and (c) in which the common duct was dilated. It has been noted that induration of the head of the pancreas may be caused by stones in the ampulla of Vater and, therefore, this sign is considered in certain cases an indication for exploration. The indurated common duct found in acute and subacute inflammation of the gallbladder and associated with only a mild degree of jaundice (icteric index of 30 or less), generally, was not opened, for it seldom contains stones. However, if the duct was distended as well as indurated, it was explored. Patients with cholecystitis and cholelithiasis, giving a history of repeated attacks of jaundice, were explored with particular care not to overlook stones, for in these cases they were frequently found in the hepatic ducts.

Stones were located and removed in 60 cases. In seven other cases, there was a stenosis or complete obliteration of the common duct. Therefore, in 67 of the 112 patients, the cause of the obstruction of the common duct was found and corrected. In the remaining 40.2 per cent of the cases, the exploration was of questionable therapeutic value (Table I).

TABLE I

SYNOPSIS OF 112 COMMON DUCT EXPLORATIONS IN 907 PATIENTS WITH NONMALIGNANT DISEASE OF THE GALLBLADDER AND BILIARY TRACT

New York Hospital, September 1, 1932, to September 1, 1938

		Stones in Common Duct	No Stones in Com- mon Duct	Deaths	Mortality Rate
Total patients	112	60	52	14	12.5%
Operations for stone	100	55	45	10	10.0%
Operations for benign stricture	12	5	7	4	33.3%

Analysis of Cases—In the series of 112 cases with obstruction of the common duct, there were 79 women and 33 men. Fourteen patients died after operation, six of whom were women and eight men. The mortality for women was 7.5 per cent and for men, 24.2 per cent. This is in keeping, in a measure, with our experience in surgery of the biliary tract in general, for the incidence of the disease is much higher in women but they, seemingly, withstand the operative procedures better than men. The mortality rate for the entire series was 12.5 per cent. An analysis of the deaths shows that the average age of the 14 patients who died was 55.7 years, the oldest was 76 and the youngest 33 years of age. Six deaths followed secondary operations. Four of these operations were for stenosis rather than stone and were, therefore, attempts to relieve an almost complete obstruction present for varying periods of time. The remaining eight deaths followed primary operations, stones were found and removed in six. One patient had an inflammatory stricture of unknown origin, while no cause for the obstruction was found in another.

Common to all patients who died was marked jaundice, and at postmortem

ten of the 14 showed evidence of marked to severe hepatic damage. The primary cause of death in six patients was hemorrhage. There was one patient, a man, age 62, in whom the failure to remove a stone at operation may be said to have contributed to death. At autopsy, 52 days after operation, a stone was found impacted in the ampulla of Vater (Table II).

Exploration of the common duct was carried out in acute as well as chronic cholecystitis. Twenty-one of the 112 patients subjected to this procedure had acute cholecystitis, and in nine, stones were removed, in the other 13, no stones were found. The opening of the common duct, when stones were not present, in no case resulted in a fatality, but it cannot be said that it did not contribute to prolonged hospitalization. There was only one death in this group of cases, the mortality rate was, therefore, 4.5 per cent, much lower than that for the entire series. This may be accounted for by the fact that the average age in these patients was relatively low, lower than the average for the entire series, and the disease, therefore, may have been of shorter duration.

The common duct was explored in 78 patients with chronic cholecystitis, and stones were found and removed in 46, not found in 32 cases. There were nine deaths in this group. Almost without exception the diseases of the gallbladder had existed for a long time. Many of the patients gave histories of symptoms for 30 years with repeated attacks of jaundice. Several patients had had previous cholecystostomies or partial cholecystectomies, and in some a stone has been overlooked at a former operation. This latter situation arose four times in our experience, but for the most part the patients had been operated upon elsewhere, primarily. No doubt other hospitals see patients in whom we have overlooked stones.

In the remaining 12 cases of the series, secondary operations were performed for stenosis of the common duct. These patients previously had had a cholecystectomy or an exploration of the common duct and at operation were found to have a partial stricture or complete stenosis of the duct. In one instance, an exhaustive search revealed only a bulb-like sacculation at the junction of the hepatic ducts, in the place of the common duct. A definite history of injury to the duct at a previous operation was obtained in five cases. In three other patients, a technical error, apparently, had been overlooked by the operator and, in the remaining four, the history was inadequate or unsatisfactory.

Although the marked stenosis appeared to be the principal cause of obstruction of the duct in this group of cases, there were five in which stones were found and removed. In one patient the stenosis of the common duct appeared to be caused by distortion, the result of contracture of the scar of an old sinus tract. The mortality rate for these cases was 33.3 per cent (Table III).

One method we employ in the treatment of stenosis of the common duct may briefly be described. It consists in excision of the constricted portion of the duct and reestablishment of its continuity by an end-to-end anastomosis

TABLE II
ANALYSIS OF DEATHS

Case Number	Sex	Age	Jaundice	Operation	Findings in Common Duct	Cause of Death
1 33617	M	62	+	Cholecystectomy Choledochotomy	2 stones in common duct, 1 found at autopsy	Subphrenic abscess, biliary cirrhosis
2 159038	M	57	+	Cholecystectomy Choledochotomy	2 stones	Hemorrhage, erosion of portal vein
3 144652	M	53	+	Cholecystectomy Choledochotomy	Cast of stones	Bronchopneumonia, pulmonary embolism*
4 7460	M	44	+	Cholecystectomy Choledochotomy	16 impacted stones	Biliary cirrhosis, hemorrhage
5 46479	F	33	+	Cholecystectomy Choledochotomy	Stones impacted in ampulla	Hemorrhage, pulmonary edema
6 66841	F	67	+	Cholecystectomy Choledochotomy	No stones, inflammatory stricture	Cholangitis, abscesses, common duct obstruction
7 164530	M	50	+	Cholecystectomy Choledochotomy	No stones	Bronchopneumonia, shock*
8 60269	M	52	+	Cholecystectomy Choledochotomy	Stones in duct	Biliary stenosis, shock, cirrhosis*
9 80467	M	54	+	(1) Cholecystostomy (2) Choledochotomy, cholecystectomy	9 stones	Hemorrhage, choleduodenocolic fistula, abscess
10 92056	M	54	+	Cholecystectomy Choledochotomy	No stone in common duct, stone in liver bed	Necrosis of urinary bladder wall, multiple hepatic abscesses
11 62321	F	41	+	(1) Cholecystectomy and choledochotomy 4 mos previously (2) Choledochotomy for stenosis	Stenosis	Hemorrhage, biliary cirrhosis
12 93439	F	53	+	(1) Cholecystectomy 1 yr before (2) Choledochotomy	Complete stenosis	Hemorrhage, biliary cirrhosis with central necrosis
13 107763	F	65	+	(1) Cholecystectomy 1 yr before (2) Attempted choledochotomy	Complete stenosis	Hemorrhage, biliary cirrhosis
14 202305	F	76	+	(1) Perforation—fistula 6 yrs before (2) Excision fistula, choledochotomy	Stone in duct	Cholangitis, central necrosis of liver

* No autopsy

TABLE III

SYNOPSIS OF 112 CASES OF EXPLORATION OF THE COMMON DUCT FOR OBSTRUCTION

	Total	Stones	No Stones	Deaths	Mortality Rate
Acute Cholecystitis	22	9	13	1	4.5%
Chronic cholecystitis and primary operations	78	46	32	9	11.5%
Stenosis of the common duct	12	5	7	4	33.3%

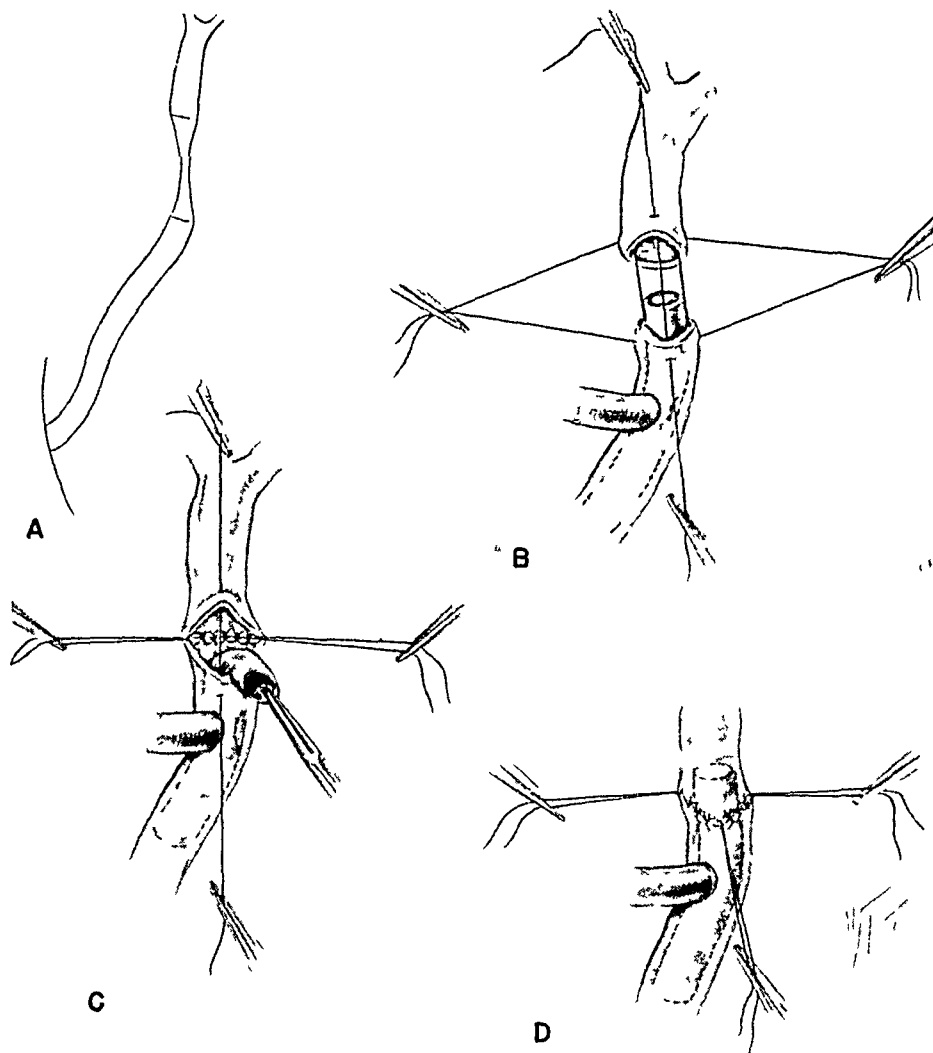


FIG. 1.—End to End Anastomosis of Common Duct. A Schematic drawing of stenosed common duct. B Stenosed area has been resected, ends mobilized, T tube inserted in distal portion, and three stay sutures of arterial silk placed. C The placing of interrupted sutures in anastomosis. D Anastomosis complete.

Figure 1, A, B, C and D, shows the following stages of the procedure

Figure 1A shows a schematic drawing of the common duct constricted in the region of the cystic duct, the most common site for strictures

Figure 1B shows the duct after the cicatrix has been excised. The prox-

imal and distal ends of the duct have been mobilized by dissection for a distance of 4 cm. Three arterial sutures have been placed in the wall of each stump, by tension on these, the resected ends of the duct are approximated. An incision is made in the distal portion of the duct to introduce a T-tube, the proximal end of this tube will extend across the suture line.

Figure 1C. Interrupted arterial silk sutures are used to make the anastomosis between the two ends of the duct. Placing these sutures is facilitated by the stay sutures which were introduced earlier.

Figure 1D shows the anastomosis with the T-tube in place.

A second method which we have used in treating stenosis of the common duct may be presented by citing a case in which a lateral-transverse anastomosis between the biliary tract and the duodenum was made to reestablish a passage for the bile.

Case Report—Hosp. No. 212,197. H. S., white, female, age 61, married, was admitted to the New York Hospital, September 7, 1938, complaining of jaundice. Her previous history was not significant except for jaundice. Her present illness dated back five years, at which time she suffered indigestion with gaseous eructations after meals and a sensation of fulness in the epigastrium. Two years before we saw her, she noticed for the first time a generalized pruritus followed by a progressively deepening jaundice. She also noted anorexia, clay-colored stools and dark urine, but she had no pain. An exploration of the common duct was made at this time, and the operating surgeon reported that the gallbladder appeared normal but that it was distended. He found a lesion in the common duct, midway between the cystic duct and duodenum, which he believed to be malignant, this, however, was not proven by biopsy. He opened the duct and drained it, leaving the gallbladder in place. The patient's postoperative course was uneventful. She drained bile for several weeks, after which the tube came out and the sinus tract closed. The jaundice did not immediately reappear, but over a period of 18 months postoperatively, she had occasional transient attacks of painless jaundice. Six months prior to admission to the New York Hospital, the patient again noticed signs of biliary obstruction. She became jaundiced, lost 34 pounds in weight and had anorexia. On admission to the hospital she was markedly jaundiced, there was no bile in her stools but bile was present in her urine. It was our impression, before operation upon this patient, that she had a benign stricture of the common duct.

Operation—September 9, 1938. A distended gallbladder was found which contained grayish fluid. On palpation, the common duct was extremely hard and slightly irregular in outline from where it entered the duodenum to a point just above its junction with the cystic duct. Above this point the biliary tract was distended. An incision was made into the common duct and yellow bile obtained. A section of the indurated portion of the duct was removed for microscopic examination, which failed to show malignancy but was thought to consist of fibrogranulomatous tissue. A rubber tube was inserted into the patent portion of the common duct and through this the entire output of bile drained for 87 days. All the bile was collected and ingested by the patient.

Second Operation—December 5, 1938. A lateral-transverse choledoduodenostomy was performed as follows. The common duct was freed from adjacent structures from the junction of the hepatic ducts to the cystic duct. The duodenum was mobilized and displaced upward by incising the peritoneum posteriorly along its second portion near the common duct. The site in the common duct selected for the anastomosis was about 2 cm from the bifurcation and the site in the duodenum, 10 cm from the beginning of its second portion, these areas of the two structures were held in approximation by stay sutures. An anastomosis was then made between the duct and duodenum by the technic described.

by Halsted for gastro-enterostomy. The opening into the common bile duct was longitudinal and that in the duodenum transverse. A fine silk, continuous suture brought the serosal surfaces together, while a continuous lock suture of No 00 catgut included all layers of duodenum and common duct. Fine silk was used for mattress sutures. Upon completion of the anastomosis, a stoma, about 1 cm in diameter, could be demonstrated between the two structures (Fig 2). The wound was closed without drainage. The postoperative course was satisfactory and, during the four months since operation, the patient has been free of symptoms and has regained her original weight. Her icteric index is normal.

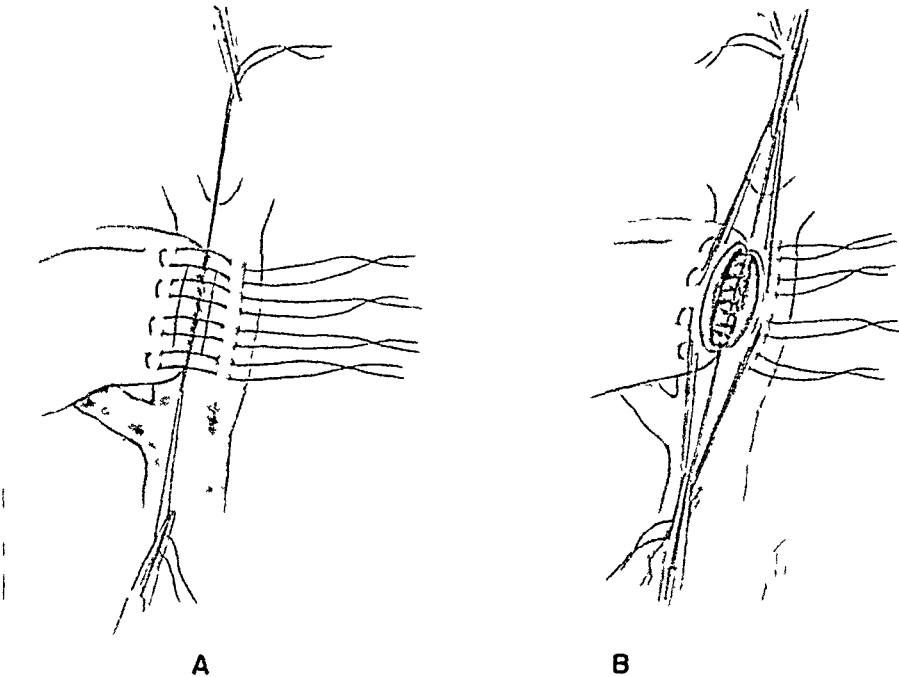


FIG 2—Lateral Transverse Choledoduodenostomy. A Duodenum approximated to common duct by continuous suture of arterial silk. Mattress sutures have been placed. Lines indicate incision. B Anastomosis with incisions and posterior wall completed.

In justification of the procedure described, and in answer to the criticism that infection might travel up through the stoma from the duodenum, it may be said that the contents of the duodenum tend to flow through the mesenteric portion of the lumen and, therefore, there is little danger of reflux of partially digested food into the common duct.

It may be of interest to describe some simple aids which we have employed with some success in surgery of the common duct. Since it has become known that bile taken by mouth replaces to some degree the bile lost from the intestine by obstruction of the common duct, it seemed important to devise a simple method for the collection and preservation of bile from a biliary fistula. The draining sinus, usually located in the upper part of the right upper quadrant, is covered by a rubber cup such as is used by urologists to collect urine from a ureteral fistula. To make them adhere closely, the skin and rubber surfaces are cleansed thoroughly and coated with tincture of benzoin. The cup is kept immobile by an elastic belt. If the belt or the cup is

placed too high so that the patient is made uncomfortable by pressure over the costal margin, he will be tempted to slip them down. Once the cup is dislodged from its original position, a water-tight junction is jeopardized. The rubber outlet tube leads from the dependent portion of the cup to a urinal bag which the patient wears on his right thigh. This bag, enveloped in a cloth sack, is kept in place by a strap worn over the shoulder. It has a

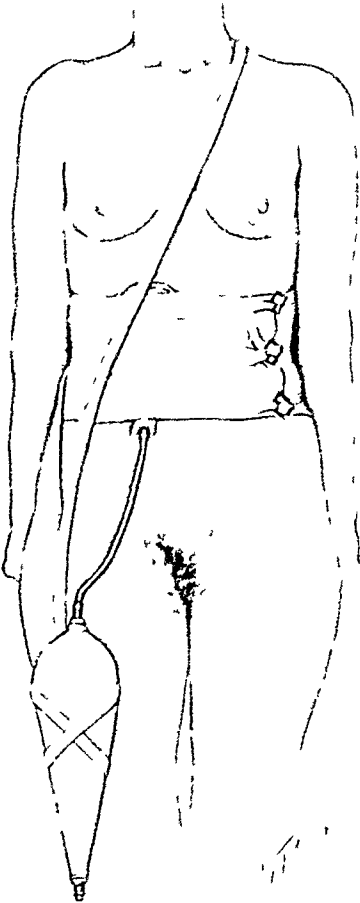


FIG 3—Collection of Bile from a Biliary Fistula. The rubber cup, held in place by an elastic belt, receives the bile from the fistula, which is then delivered into a rubber bag.

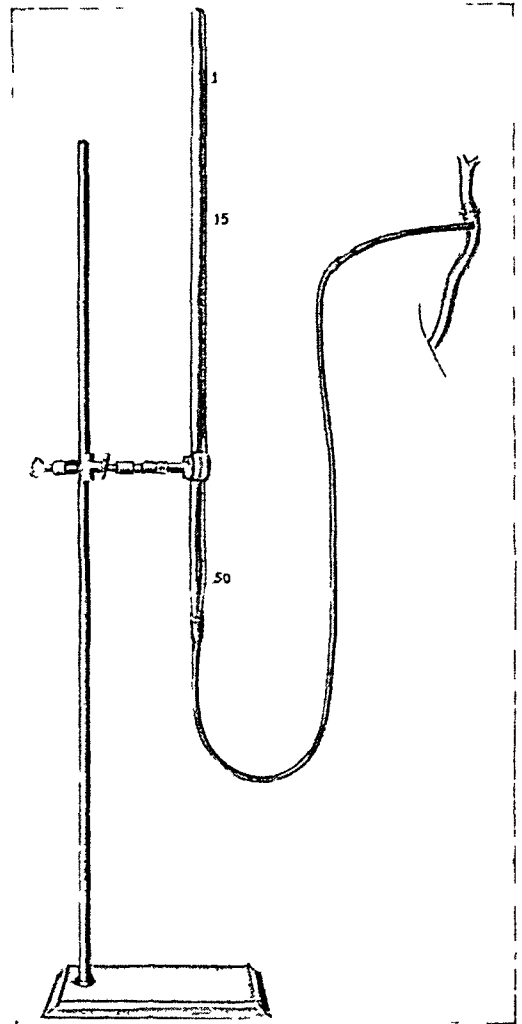


FIG 4—A 50 cc burette on an adjustable support serves as a reservoir to vary the pressure within the common duct.

capacity of 250 cc, which necessitates emptying it four times during 24 hours (Fig 3). At night, the drainage of bile has been found to be considerably less in amount but more concentrated than by day, therefore, the patients must be instructed to collect the night as well as the day drainage. At night, the rubber tube leading from the cup is connected to a bottle suspended at the side of the bed. Since, in the recumbent position, the cup is likely to overflow and the bile leak out between it and the skin, the bottle is supplied with low grade suction by an attachment to a water faucet.

The bile is stored in glass receptacles and placed on ice. It should be filtered to remove debris and pus, but need not be treated with preservatives. The patient ingests the bile between meals in five or six equal parts during the

24 hours The average output of bile in a normal subject, weighing 150 pounds, is between 800 and 1,400 cc during 24 hours (Chart 1)

An obstruction in the distal portion of the common duct which persists after exploration and removal of stones is not an infrequent occurrence It is believed to be caused either by edema or spasm in the lower portion of the duct or at the ampulla The edema probably is due to infection, physiologists have not as yet explained spasm in the region of the ampulla of Vater Certain clinicians³ have recommended instrumental dilatation of the ampulla at the time of exploration in order to prevent later spasm This procedure is considered too dangerous because of the possible injury to the duodenum Our experience indicates that the introduction of sufficient pressure into the

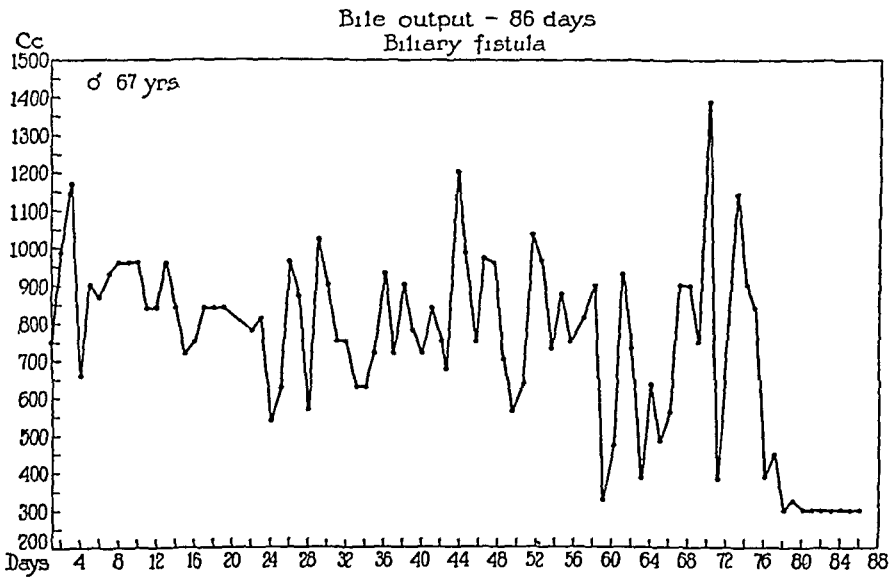


CHART 1—Hosp No 43,525. Bile output, from a male, age 67, as collected, by the method described, over a period of 86 days

drainage tube to forcefully dilate the lower segment of the duct is also contraindicated It tends to increase the intraductal pressure in the fine biliary tributaries in the liver and, thereby, to suppress the secretion of bile A much less hazardous method has been employed by us in handling this situation It requires a graduated burette, 50 cm in length, connected to the rubber drainage tube in the common duct (Fig 4) The burette is filled with saline solution and, by raising or lowering it on an adjustable support, the pressure can be reduced or increased at will Ten to 15 cc of pressure usually suffices to overcome the obstruction at the lower end of the duct

A very promising contribution to surgery of the biliary tract, and of the common duct in particular, has been the introduction of vitamin K and bile salts for the prevention and control of hemorrhage in jaundice In jaundiced patients, the clotting and bleeding times are usually normal, but the clot retracts poorly and is fragile, thus, it does not seal the open end of the vessel well and bleeding follows straining or coughing The fundamental defect which causes this condition was found to be a deficiency in prothrombin in

the blood, and a test has been devised to determine the amount of this substance present. It was demonstrated that if prothrombin is reduced to 30 per cent, or less, of the normal quantity, there was a marked tendency to bleed.⁴ Further, it was found that chicks on a deficient diet developed a hemorrhagic tendency which could be overcome by a substance contained in alfalfa, which was determined to be vitamin K. Dogs with a biliary fistula showed a similar tendency to bleed. In both experimental animals, the administration of vitamin K and bile salts by mouth led, almost invariably, to an elevation of the prothrombin level and a correction of the bleeding tendency.

Absence of bile from the intestinal tract interferes with the digestion and absorption of fats. Vitamin K, which probably is a steroid and soluble in lipoids, therefore, requires the presence of bile salts to make it effective, for without them it will not be absorbed from the intestinal tract into the blood stream, and will not, therefore, reach the liver, where, it is believed, it is converted into prothrombin.

In view of these findings by different investigators throughout the country, we have felt that any patient with jaundice who requires operation should have a prothrombin determination. If the prothrombin level is below 60 per cent of normal, vitamin K and bile salts should be administered. Depending on whether the liver has been damaged or not, there will be a rise in the prothrombin level to normal and a reduction in the tendency to bleed. When there is marked damage to the liver, this return to normal will proceed more slowly, if at all.

An interesting report of clinical experiences with the administration of vitamin K and bile salts from the Mayo Clinic shows that of 28 patients with jaundice, to whom this therapy was administered before and after operation, only three bled at all, and those not severely. Of 14 cases to whom bile salts and vitamin K were not given, 64 per cent bled after operation.

During the past few years, clinical and laboratory investigations on jaundice have been carried on in our departments of Surgery and Pathology, which confirm the findings of other investigators. Two patients have been selected from 17 jaundiced cases, as examples of the clinical value of bile salts and vitamin K. The course of their disease is shown in Charts 2 and 3. The first case is typical of untreated jaundice—lowered prothrombin level—bleeding tendency—hemorrhage and death (Chart 2). The second case had deficient prothrombin, but by the administration of bile salts and vitamin K it was elevated before operation, however, it fell after the operative procedure. Toward the end of her long stay in the hospital, the course of the prothrombin content of the blood was upward without therapy (Chart 3). The third chart is that of a patient with biliary obstruction who responded well to therapy (Chart 4).

The credit for this interesting and valuable contribution to surgery of the common duct belongs to Dam,¹⁹ Greaves and Schmidt,²⁰ Quick, Stanley-Brown and Bancroft,⁵ Kugelmass,⁷ Almquist and Stockstad,⁶ Brinkhaus,⁸ Smith and Wainer,⁹ the Mayo Clinic¹⁰ and Andrus, Moore and Lord.¹¹

CASES ILLUSTRATING THE USE OF VITAMIN K AND BILE SALTS
IN COMBATING THE HEMORRHAGIC TENDENCY IN JAUNDICE

During the past few years, clinical and laboratory investigations dealing with jaundiced patients have been carried on, in the departments of Surgery and Pathology of the Cornell Medical College and the New York Hospital, by Doctors Andrus, Moore, and Loid, and the following data have been obtained from them. Charts of three patients are presented. One of the patients selected was studied before vitamin K was available (Chart 2) and is offered for comparison with two jaundiced patients who received vitamin K

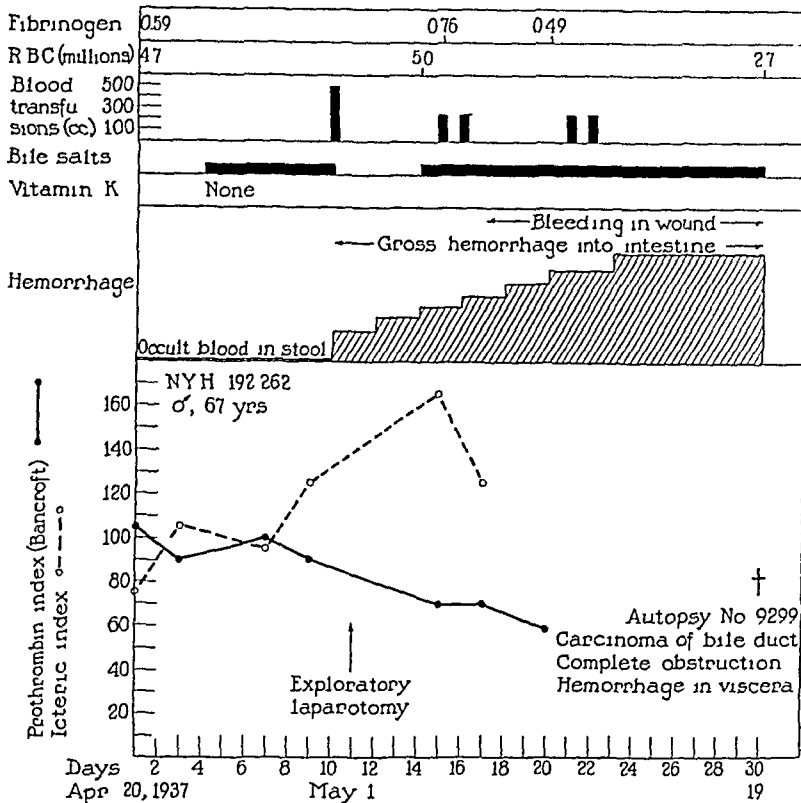


CHART 2—Hosp No 192,262. A jaundiced patient studied before vitamin K was available. Transfusions and bile salts completely failed to control the increasing hemorrhage.

and bile salts (Charts 3 and 4). These two patients were selected from a group of 17 who were jaundiced, had a lowered prothrombin, and were considered, therefore, as having a tendency to bleed. These were treated with vitamin K and bile salts, none bled seriously after operation. (The complete study will be published later.)

In reviewing what has taken place since the introduction of choledochotomy, less than 50 years ago, we may find some encouragement in the realization that important lessons have been learned. We know the value of a thorough exploration of the extrahepatic biliary tract in primary operations for disease of the gallbladder; we have, in the majority of cases, abandoned cholecystostomy in favor of cholecystectomy. When the common duct is opened and

explored for stones, we know that the patient's best interests are served if the duct is drained. We have learned that a tendency to bleed in jaundice may be lessened by correcting the low prothrombin content of the blood and that this may be accomplished by administering vitamin K and bile salts.

These many contributions to successful surgery of the biliary tract do not answer two fundamental questions—as to how to diminish the incidence of obstruction of the common duct and how to avoid overlooking stones. In regard to the first question, some data which we have assembled may be significant. The average age of the patients with stones in the common duct was over 50 years, the average age of those who died was 55.7 years, a long history of symptoms referable to the biliary tract was obtained in 60 per cent of the cases, recurrent attacks of jaundice followed by persistent jaundice in

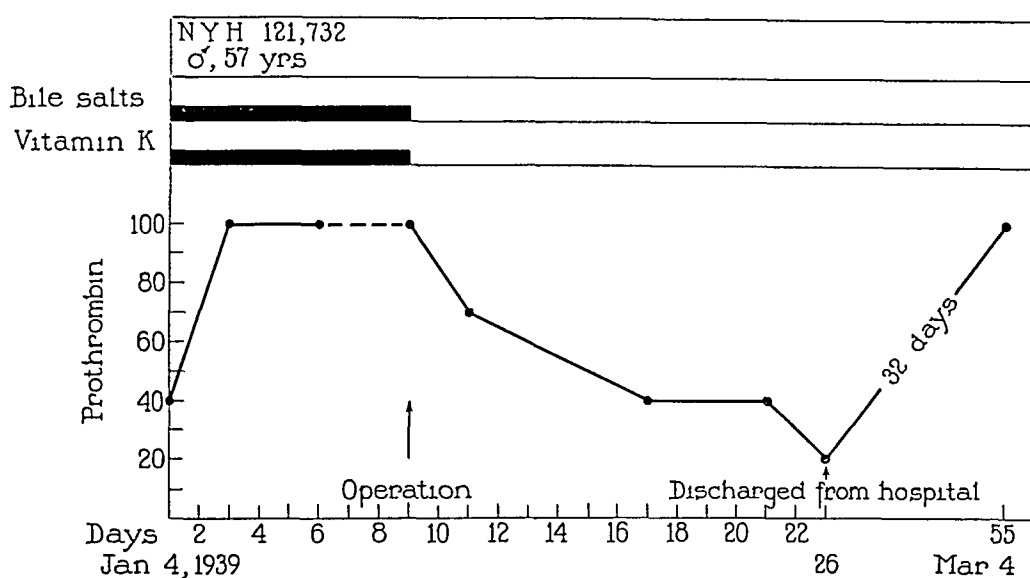


CHART 3—Hosp No 121,732. A jaundiced patient with a lower prothrombin, illustrating an excellent response to vitamin K and bile salts. A fall in prothrombin occurs after operation followed by spontaneous relevation of the prothrombin level to normal.

these patients suggested the presence of stones in the duct for long periods of time. It is generally agreed that stones almost never occur in the common duct unless they are also present in the gallbladder. In our experience, there was not one instance of stones in the common duct associated with a normal or stoneless gallbladder.

These facts would seem to indicate that common duct stones are more often associated with the late, rather than with the early, stages of disease of the gallbladder. Interruption of the progress of such disease, by early cholecystectomy, might be expected to prevent the formation of stones in the common duct.

The obstruction of the common duct which is associated with stenosis carries with it a very high mortality (33 per cent in our series). It is hardly necessary to emphasize the need of careful surgical technic in cholecystectomy, though the reduction in the incidence of injury to the common duct rests, almost wholly, upon this admonition. Stricture and distortion of the common duct may result from faulty placement of drains. We have found that it is

wiser not to attach the rubber drainage tube in the common duct either to the skin or the dressing as is frequently done, for with changes in the intra-abdominal pressure, and the position of the organs which may occur, leeway for adjustment to new positions must be left for this tube, or the common duct may be hooked up and distorted when the wound heals.

Halsted,¹² Richter and Buchbinder,¹³ 50 years ago, advocated closing the duct and the wound without drainage. We feel that until our surgical technique and skill have reached a degree of perfection which will guarantee that the obstruction in the duct has been completely removed, that the anastomosis is faultless, and that the wound, including the bed of the gallbladder in the liver, is free of traumatized tissue, we are not justified in omitting drainage after exploration of the duct.

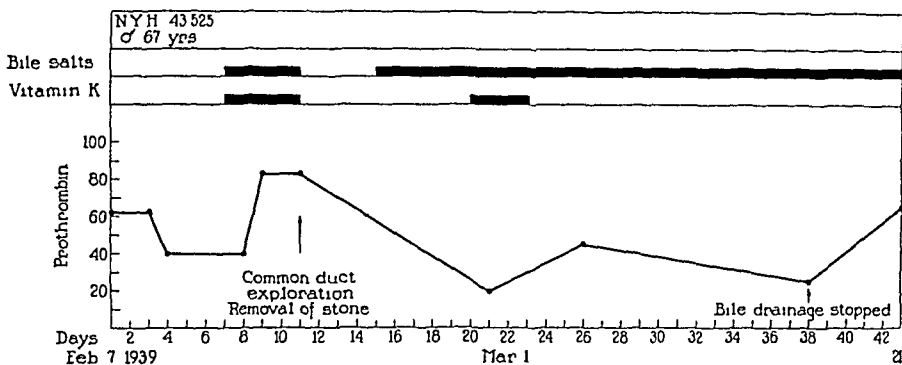


CHART 4—Hosp No 43,525. A jaundiced patient with a lowered prothrombin is given vitamin K and bile salts, followed by an elevation of prothrombin. Following operation, there is a fall with partial relevation of the prothrombin, upon additional therapy during loss of bile through a biliary fistula. After closure of fistula the prothrombin rises.

In considering the second question, it must be admitted that few surgeons, in exploring common ducts for stones, have escaped the embarrassment of finding that they have overlooked one. This accident occurs, even when all known devices to locate them have been employed. Some of these aids in exploring the duct for stones may, briefly, be enumerated. Careful palpation before and after opening the duct obviously is of great importance. When opened, the lower portion of the duct should be explored first, so as to allow stones in the upper portion to be carried down by the flow of bile. The introduction of small olive-tipped silk catheters, through which the duct may be irrigated with saline, has been advocated by Cheever.¹⁴ Free irrigation into the duodenum with saline—not always easily accomplished and sometimes impossible—also has its place. The use of spoon-shaped scoops and forceps is of value in removing stones that have been found, but is of no great benefit in locating the elusive stone. The introduction of a small electric light¹⁵ into the duct has merited some credit in our hands, by identifying several stones which had escaped notice by other methods.

Indirect methods of determining the presence of stones in the duct include roentgenologic examinations by plain films of the abdomen. Graham's¹⁶ cholecystography occasionally reveals a stone in the common duct. Visuali-

zation of the biliary tree on the operating table with the aid of opaque injections has been advocated. The method was first described, in 1925, by Cotte,¹⁷ who used iodized oil. His work was followed by investigations by Best and Hicken,¹⁸ who popularized the use of lipiodol and diodrast for this purpose. We have employed these indirect methods as accessory procedures, when careful exploration by other methods failed to reveal stones in patients in whom we suspected them to exist. These aids, however, are not infallible. Unfortunately this question of overlooking stones has not been satisfactorily answered as yet.

SUMMARY

An analysis is given of 112 cases of exploration of the common duct for obstruction. Twenty-two of the patients had acute cholecystitis at the time of operation, 78 had chronic cholecystitis, and 12, stenosis or obliteration of the common duct.

A description of two methods for the treatment of stenosis of the common duct is given.

Some simple methods in the treatment of patients with jaundice are described.

Two questions are propounded which have not as yet been satisfactorily solved.

REFERENCES

- ¹ Proceedings and Transactions of the New York Surgical Society, March 11, 1891.
- ² Proceedings and Transactions of the New York Surgical Society, October 6, 1892.
- ³ Potoschmig, G. Contributo alla chirurgia della litiasi biliare con particolare riguardo alla calcolosi del coledoco. *Arch ital di Chir*, 14, 533, 1925.
- ⁴ Lewisohn, R. Hematologic Studies as Basis for Determining Risk of Postoperative Hemorrhage in Jaundiced Patients. *ANNALS OF SURGERY*, 94, 80-87, July, 1931.
- ⁵ Quick, A. G., Stanley-Brown, M., and Bancroft, F. W. A Study of the Coagulation Defect in Hemophilia and in Jaundice. *Am J Med Sci*, 190, 501-511, October, 1935.
- ⁶ Almquist, H. H., and Stockstad, E. L. R. Hemorrhagic Chick Disease of Dietary Origin. *J Biol Chem*, 11, 105-113, September, 1935.
- ⁷ Bancroft, F. W., Kugelmass, I. N., and Stanley-Brown, M. Evaluation of Blood-Clotting Factors in Surgical Diseases. *ANNALS OF SURGERY*, 90, 161, 1929.
- ⁸ Warner, E. D., Brinkhaus, K. M., and Smith, H. P. A Quantitative Study on Blood Clotting. Prothrombin Fluctuations Under Experimental Conditions. *Am J Physiol*, 114, 667-675, 1935.
- ⁹ Brinkhaus, K. M., Smith, H. P., and Warner, E. D. Prothrombin Deficiency and Bleeding Tendency in Obstructive Jaundice and in Biliary Fistula. Effect of Feeding Bile and Alfalfa (Vitamin K). *Am J Med Sci*, 196, 50-57, 1938.
- ¹⁰ Butt, H. R., Snell, A. M., and Osterberg, A. E. Further Observations on the Use of Vitamin K in the Prevention and Control of the Hemorrhage Diathesis in Cases of Jaundice. *Proc Staff Meet Mayo Clinic*, 13, 753-764, 1938.
- ¹¹ Andrus, W. D., Moore, R. A., and Lord, J. Personal communication.
- ¹² Halsted, W. S. The Omission of Drainage in Common Duct Surgery. *Surgical Papers*, 2, 472.
- ¹³ Richter, H. M., and Buchbinder, J. R. The Omission of Drainage in Common Duct Surgery. *J A M A*, 73, 1750-1751, December 6, 1919.

- ¹⁴ Cheever, D Instrumental Dilatation of Papilla of Vater and Dislodgment of Calculi by Retrograde Irrigation Arch Surg, 18, 1069-1077, April, 1929
- ¹⁵ Glenn, F Surgery of the Gallbladder and Biliary Tract ANNALS OF SURGERY, 103, 77-84, January, 1936
- ¹⁶ Graham, E A, Cole, W H, Copher, G H, and Moore, S Diseases of the Gallbladder and Bile Ducts Lea & Febiger, 1928
- ¹⁷ Cotte, G Demonstration of Calculus in the Ampulla of Vater by Lipiodol Injection of a Biliary Fistula Lyon Chir, 22, 691-697, 1925
- ¹⁸ Hicken, N F, Best, R R, and Hunt, H B Cholangiography, Visualization of the Gallbladder and Bile Ducts During and After Operation ANNALS OF SURGERY, 103, 210-229, February, 1936
- ¹⁹ Dam, H The Antihemorrhagic Vitamin of the Chick, Occurrence and Chemical Nature Nature, 135, 652, 1935
- ²⁰ Greaves, J D, and Schmidt, C L A The Role Played by Bile in the Absorption of Vitamin D in the Rat J Biol Chem, 102, 101, 1933

DISCUSSION —DR CONDUCT W CUTLER, JR (New York) said that Doctor Glenn's paper was timely and presented much food for thought First, with regard to the practical consideration of dealing with the common duct in cases of jaundice, it is undoubtedly true—and rests within the clinical experience of all surgeons—that stones have been left in the common duct by reason of a failure to explore it except by palpation Most surgeons are exploring the duct more frequently than formerly It is true that the common duct stone is often elusive to palpation, and that where its presence may be reasonably suspected, opening of the duct must be undertaken Probably the history of recurring jaundice, where there is or has been a stone-bearing gallbladder, is the most reliable criterion for the need of this maneuver

Stenosis or stricture of the common duct, as the result of a previous operation, may cause jaundice without the presence of stones As Eliot has shown, blocking may also occur by reason of a variety of mechanical effects (other than malignancy) where stones have not been present Where such is the case correction of the pathology will suffice to cure the difficulty without need of opening the duct When stones are, or have been present, in the gallbladder with subsequent blocking of the duct, exploration alone will give assurance of their absence, even though adhesions or scarring may seem to explain the phenomenon Dinsmore says that 30 per cent of cases of jaundice are due to stones, and 30 per cent to carcinoma

It must be agreed that when the common duct has been opened for exploration it is safer to drain it In Doctor Cutler's opinion it is desirable, also in these cases, to insert a rubber tube fenestrated drain in the region of Morrison's pouch, as recommended by Whipple The T-tube in the duct is never water-tight and some spilling is bound to occur This is particularly true if any means is adopted, as recently advocated on somewhat theoretic grounds, to control mechanically the rate of drainage of bile in an effort to avoid too rapid decompression of the biliary system The spill must have free and ready access to the surface until the formation of a tract shall have protected the peritoneum from bile invasion For facilitating the removal of the T-tube, notching it at the junction of the arms is most helpful This avoids damage to the duct when the tube is pulled out Also, the tube must not be too stiff Ochsner's flexible probe has proven the most useful instrument for exploring the patency of the ampulla

Of great importance is the matter of preparation of the jaundiced patient for operation The use of bile salts preoperatively, supplemented with vitamin K, especially when the diet has been deficient, is fulfilling its promise as

a useful safeguard against bleeding through its effect on prothrombin. The status of calcium as a deterrent to hemorrhage is debatable. Almost certainly, it does no harm, and Doctor Cutler said that he continues to use it as a possible help. In the enthusiasm for newer aids, older ones must not be lost sight of. The preliminary supply of adequate fluids for the patient's tissues, by repeated infusions before operation, is still an essential. So also is the attempt to aid the damaged liver by providing, through the use of glucose in the infusions, an adequate glycogen reserve. Transfusions is of notable aid to the jaundiced patient. After operation, introduction of the Levine tube has been found helpful in controlling vomiting and relieving gastric distention. It is coming into frequent use as a prophylactic measure.

These practical measures, new and old, plus such technical care and ingenuity in the performance of the operative procedure as Doctor Glenn has advocated in his paper, will continue to bring about improvement as regards morbidity and mortality in this group of seriously ill patients.

DR FRANK GLENN (closing) said that he had been influenced to explore the common duct on slight indication in the hope that a stone would not be overlooked. He felt that choledochotomy should be undertaken when there is a demonstrable cholelithiasis or a history of cholecystectomy with one or more of the following indications present: (1) When stones are palpable in the common duct. (2) When there is a history of progressive or of repeated attacks of jaundice. (3) When the common duct is dilated. (4) Sometimes when the head of the pancreas is indurated.

A history of jaundice is sometimes misleading. An indurated common duct may appear slightly distended, as seen in acute cholecystitis. There may be an icterus index of 30 without common duct obstruction. An accurate history is of great importance in considering exploration of the common duct.

It is encouraging to note that since the introduction of vitamin K and bile salts during the preoperative period, 17 patients with marked jaundice have been subjected to operation without significant bleeding.

CYSTS OF THE MESENTERY *

EDWARD W. PETERSON, M.D.

NEW YORK, N. Y.

SINCE PUBLISHING³ an account of six cases of mesenteric cysts and one case of omental cyst, operated upon without mortality, it has been my privilege to operate upon another omental cyst, and later upon an enterogenous cyst, not, however, intramesenteric in position. The patient to be shown to-night was Case 4 in the series already reported.³

Case Report—S. S., male, age 55, born in Russia, was admitted to the Post-Graduate Hospital, October 15, 1929, complaining of gradual loss of weight (15 pounds) and strength, increasing constipation, with subacute attacks of intestinal obstruction. Appetite poor, digestion fair, some nausea, but no actual vomiting. No blood or pus in stools. Symptoms began about six months ago. After roentgenologic study of the gastro-intestinal tract, in a Brooklyn hospital, a diagnosis was made of "carcinoma of the ascending colon."

Physical Examination revealed nothing of importance except upper respiratory irritation from excessive smoking of cigarettes. The abdomen showed considerable tumefaction on the right side about opposite the umbilicus, and the diagnosis of carcinoma of the colon seemed probable.

Operation—October 17, 1929. Under spinal anesthesia, the abdomen was opened through a right rectus incision. A large, hard mass was immediately encountered, but it was found to involve the ileum and not the large intestine. Coils of small intestine were adherent about the tumor, which, at the time of operation, was thought to be a new growth in the ileum, with extensive metastases in the mesentery. The involved bowel and mesentery were resected widely, followed by an end-to-end suture anastomosis. The patient stood the operation well, but convalescence was stormy. He made a good recovery finally, except for an incisional hernia.

Pathologic Report (Dr. Nicholas M. Alter). *Gross*—"Specimen consists of a large portion of the small intestine with mesentery attached. It measures 280 cm. (about nine and one-half feet) in length. The loops of the small intestine are moderately distended and are firmly adherent to a central mass which seems to come up from near the ileum about 15 cm. from the surgical stump of the ileum and from this extends into the mesentery which is adherent to the other loops of the intestine. This mass is very hard in consistency and measures about 10 cm. in diameter. On opening the bowel, no obstruction is encountered. The lumen of the ileum is free. From the ileum a cystic cavity is opening which has an orifice 6 cm. in diameter. This leads into a somewhat larger cavity which contains a great deal of greenish vegetable matter, a large amount of mucus and broken-down necrotic material and the wall is covered with a polypoid growth which is very hard at the base and on section shows a gray translucent appearance. The growth is very hard, almost cartilaginous."

Microscopic—Section of the growth shows neoplastic proliferation of small polygonal cells with large vesicular nuclei. The cells are quite anaplastic, show great variety of size and shape and form a rather diffuse growth. There is a suggestion only here and there of glandular structures and there is a vascular stroma. The growth ulcerates over

* Read before the New York Surgical Society, March 8, 1939. Submitted for publication April 18, 1939.

the mucosa and infiltrates the muscle layer, but has a rather sharp border *Pathologic Diagnosis* Embryonal carcinoma of mesenteric cyst

COMMENT—Doctor Altei's microscopic report in which he says "the growth ulcerates over the mucosa and infiltrates the muscle layer," and the observation that there was an opening from the ileum into the cyst leads us to believe that we had to deal with an embryonic mesenteric cyst, of intestinal origin, which subsequently underwent malignant degeneration. Cystic malignant disease of the mesentery is not uncommon, but malignancy developing in an enterogenous mesenteric cyst is both interesting and rare. I can find no record of a similar case. It is gratifying to have the patient remain well (except for the incisional hernia), for nearly ten years after a massive intestinal resection for the removal of an enterogenous mesenteric cyst which had become malignant.

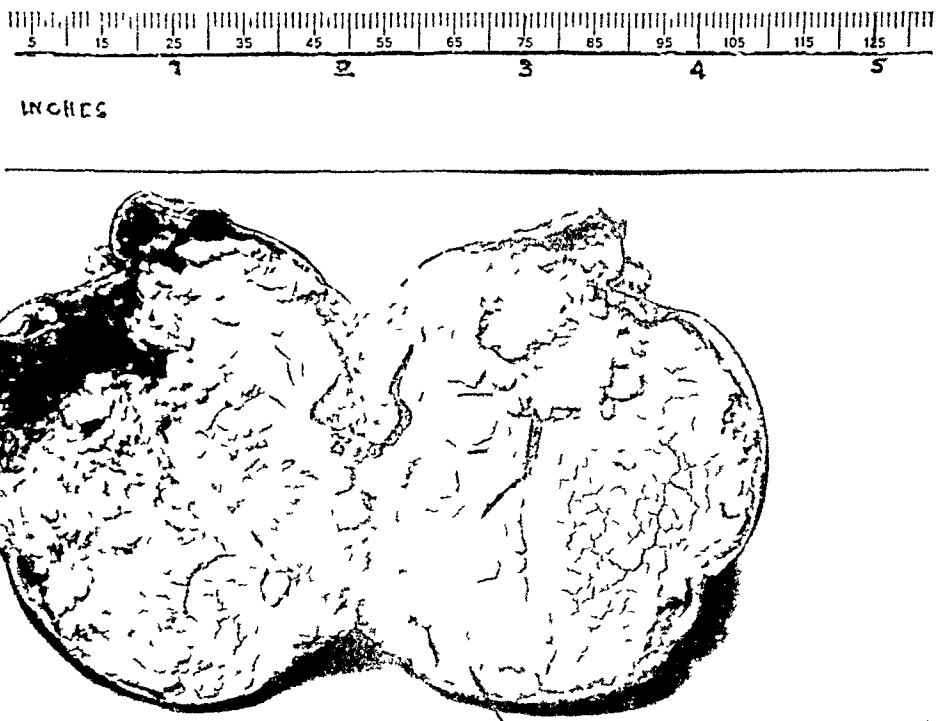


FIG 1—Shows a mesenteric cyst filled with sebaceous material

Mesenteric cysts occur somewhat more frequently in the female than in the male sex. They have been found at all ages—in the fetus and in an octogenarian. They may be single or multiple, unilocular or multilocular, and may vary in size from that of an olive to enormous growths filling the abdominal cavity.

Preoperative diagnosis is seldom made, since there are no signs or symptoms pathognomonic of mesenteric cysts. In my series a correct preoperative diagnosis was made only in my fifth and sixth cases.

Intestinal obstruction, either acute or chronic, is the most important and frequent complication of mesenteric cysts. Other complications are (1) Hemorrhage into the cyst, (2) torsion of the cyst, and (3) rupture of the cyst. The original histologic picture may be so altered from hemorrhage,

pressure, inflammation or malignant degeneration that it is difficult for the pathologist to render a satisfactory report as to the origin and structure of the cyst

True mesenteric cysts are not malignant, parasitic, or tuberculous, therefore, we must separate all cysts of the mesentery into two groups

I *Embryonic* (a) Cysts arising from embryonic remnants and sequestered tissue—(1) serous, (2) chylous, (3) sanguineous, and (4) dermoids

(b) Cysts of intestinal origin—(1) by sequestration from the bowel during development, (2) from Meckel's diverticulum, when it arises from the



FIG 2—Shows multiple cysts of the mesentery, of embryonic origin

concave side of the bowel or (as Miller has added) acquired an intramesenteric position

(c) Cysts arising from urogenital organs (germinal epithelium, ovary, wolffian body, or mullerian duct)

II *Pseudocysts* (1) Of infective origin—hydatids, and cystic degeneration of tuberculous nodes, (2) cystic malignant disease

The treatment of mesenteric cysts can be considered under the following headings (1) Enucleation, (2) removal of cyst, with bowel resection, and (3) marsupialization-drainage

(1) Enucleation This is the ideal operation and should be the method of

CYSTS OF THE MESENTERY



FIG 3 —Shows the incision into the mesenteric peritoneum over the cyst

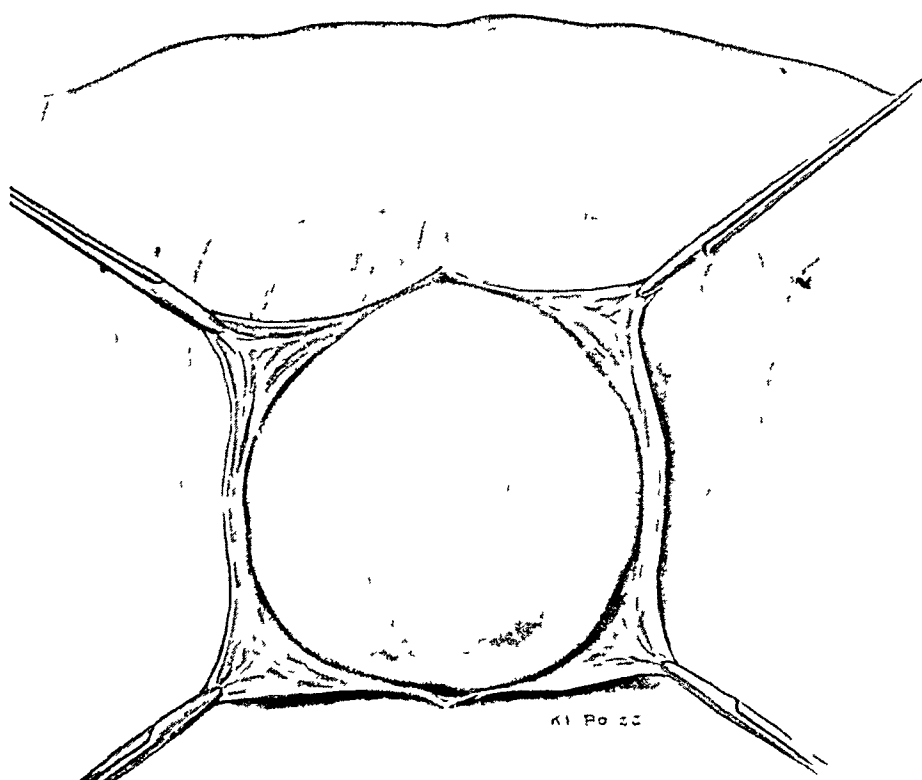


FIG 4 —Shows the cyst protruding through the incision in the mesentery

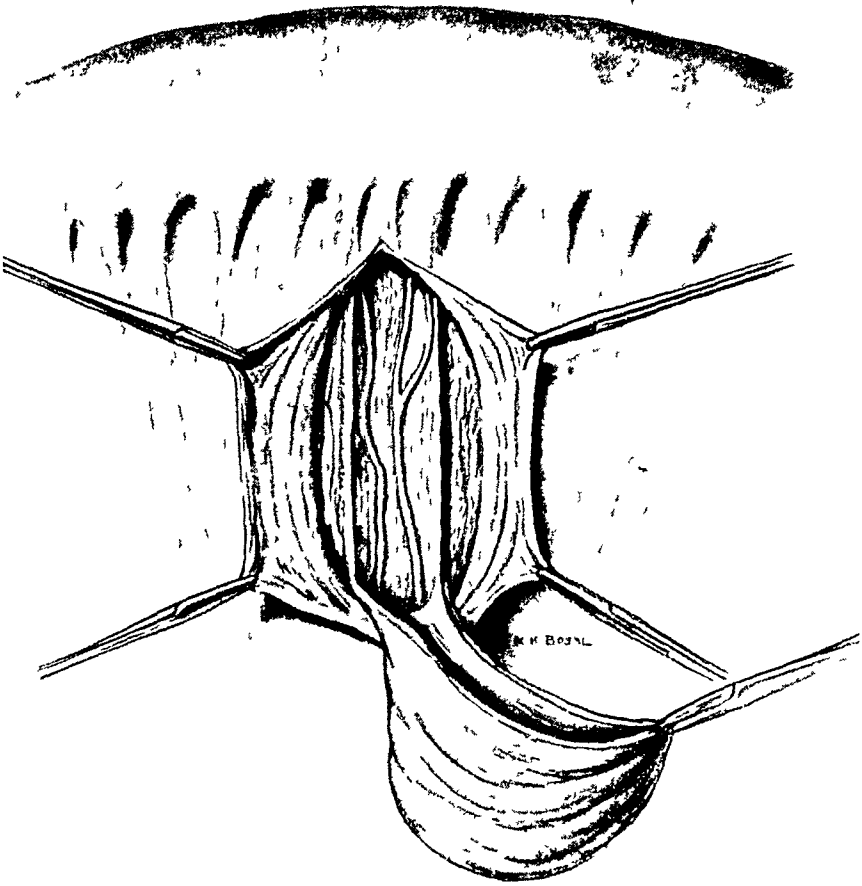


FIG 5—Shows a small segment of the cyst wall, with vessels undisturbed. The major part of the cyst wall is shown being removed.

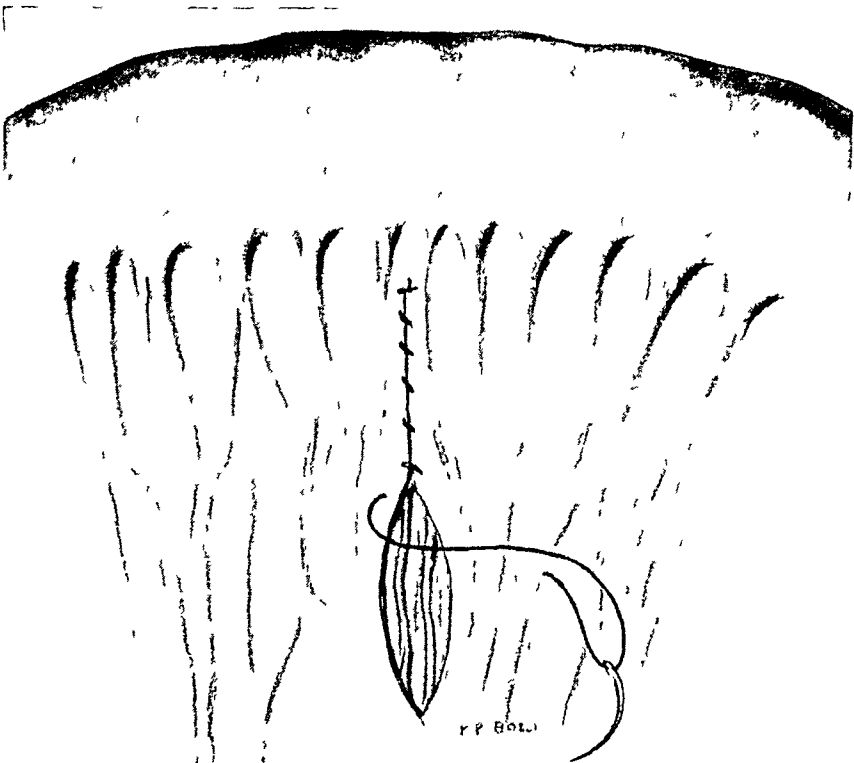


FIG 6—Shows the suture of the mesenteric incision for bringing raw mesenteric surface into contact with the remains of the cyst wall.

choice when and where it can be accomplished without damage to the bowel or to the vascular supply thereof. Enucleation could be performed in but one of my cases.

(2) Removal of Cyst with Bowel Resection. By resection is meant the extirpation of the cyst or cysts and the resection of the involved bowel, with the establishment of some type of intestinal anastomosis. This operation is often called for—probably in one-fourth to one-third of the cases encountered. Unfortunately, the mortality following resection is high—about 60 per cent. This can be explained by the fact that many of the emergency operations in which it is done are performed for the relief of acute intestinal obstruction, or in the presence of acute peritonitis. It is indicated when a successful enucleation cannot be completed and when marsupialization-drainage does not relieve or is apt to be followed by intestinal obstruction. Resection was performed in two of my six cases.

(3) Marsupialization-Drainage. When the size of the cyst, dense intestinal adhesions, or other complications make the removal of the tumor a dangerous procedure, then some form of drainage of the cyst is called for. Simple wick or tube drainage is, in my opinion, inferior to gauze packing of the cyst cavity. Carter,¹ Swaitley⁷ and others consider marsupialization obsolete, save in very exceptional instances. Flynn² thinks it applicable only in parasitic cysts or in large unilocular cysts where the removal of the tumor is extremely hazardous. Despite the immediate theoretic dangers (of infection, peritonitis, intestinal obstruction) and the possible remote complications (recurrence of the cyst, persistent sinus, hernia, late intestinal obstruction, *etc.*), a study of the many isolated case reports in which this method was employed, with both early and late good results, is convincing proof that the objections to it are more fanciful than real. It should never be employed in dermoid cysts or as a makeshift or "way out" when enucleation can be accomplished or when bowel resection is indicated. It is relatively safe and simple, with a mortality and a morbidity that is surprisingly slight. Marsupialization-drainage was employed in two of my cases.

Is there no other plan of surgical treatment to be employed, when enucleation cannot be accomplished, when bowel resection, with its high mortality, should be avoided, and when drainage, with its protracted convalescence, is deemed inadvisable? In my first case, enucleation of a mesenteric cyst could not be completely accomplished without sacrificing a relatively large blood vessel, which was feared would result in gangrene of a small area of intestine. Rather than perform a bowel resection, the major portion of the cyst was removed, leaving behind only a small segment containing the blood vessel. Carbolic acid (followed by alcohol) was applied to the strip of cyst membrane, which was brought up to the abdominal incision, and the wound was closed, except for a small gauze drain which went down to the remains of the cyst. Healing was prompt, and without sinus formation or recurrence of the cyst. In selected cases of single, thin-walled, serous, sanguineous or chylous cysts, the removal of the greater part of the cyst membrane, with closure of the inci-

sion in the mesentery, bringing the remaining segment of cyst in contact with raw surface of the mesentery, will, it is believed, prove a successful procedure. The abdomen could then be closed, in the majority of instances, without drainage.

REFERENCES

- ¹ Carter, Ralph M. Cysts of the Mesentery. *Surg, Gynec and Obstet*, 33, 544-548, November, 1921.
- ² Flynn, Charles W. Mesenteric Cysts, with Report of a Case of Cystic Lymphangioma. *ANNALS OF SURGERY*, 91, 505-513, April, 1930.
- ³ Peterson, Edward W. Mesenteric and Omental Cysts. *ANNALS OF SURGERY*, 96, 340-349, September, 1932.
- ⁴ Peterson, Edward W. Adenocarcinoma in a Cyst of the Transverse Mesocolon. *ANNALS OF SURGERY*, 97, 782-783, May, 1933.
- ⁵ Swartley, William B. Mesenteric Cysts. *ANNALS OF SURGERY*, 85, 886-896, June, 1927.

DISCUSSION.—DR FENWICK BECKMAN (New York) said that on the Children's Surgical Service at Bellevue Hospital there had been two cases of mesenteric cysts. One, a case of chylous cyst, which could not be excised, was marsupialized and finally the wound healed. It was felt there probably would be a recurrence but, so far as is known at present, there has been none. The second case occurred in a little girl operated upon by Doctor Beekman some years ago, and presented before this Society, which proved to be an enterogenous cyst situated at the angle of the ileum and the ascending colon. The child was admitted to the hospital with chronic intestinal obstruction. The diagnosis, at that time, was chronic intussusception. At operation this cyst was found, and an attempt was made to enucleate it. During the enucleation it was opened and found to contain a very thick mucus. Failing to enucleate it, Doctor Beekman marsupialized the cyst, and sutured its wall to the abdominal wall. Two or three days later feces were discharging through the marsupialized cyst. All mesenteric cysts of enterogenous nature are claimed to arise from a diverticulum—the mucous membrane being forced out through the fibers of the muscularis and carrying serosa with it, so that finally it forms a cavity outside the lumen of the intestine, and finally the connection with the lumen is obliterated entirely and the cyst becomes isolated. This cyst, which Doctor Beekman reported, one might say was in a stage of isolation. Doctor Peterson has given us a very interesting classification of these cysts. Doctor Beekman said he had always looked upon true mesenteric cysts as of three types: chylous, enterogenous and dermoid.

LEUKOPLAKIC VULVITIS *

THOMAS D SPARROW, M D

CHARLOTTE, N C

PROBABLY the first report of a case of leukoplakia involving the vulva was made by Weir,³⁶ in 1875. Ten years later, Bielsky⁴ described an atrophic shrinking of the skin involving the labia minora, frenulum, and clitoris to which he gave the name kraurosis. Szász³⁰ expressed the opinion that both of these conditions were manifestations of a single process. Berkley and Bonney² very emphatically disagreed with Szász and affirmed that the two conditions were unrelated. As time passed, many authors described similar pathologic processes and almost invariably gave a new name to the condition. In 1923, Taussig³¹ recommended the name leukoplakic vulvitis, which he felt was descriptive of the more important pathologic manifestation of the disease. In 1929, Graves and Smith¹² thoroughly reviewed the subject and selected the name kraurosis. They frankly admitted the inadequacy of their choice of name, but justified their selection on the ground that kraurosis was a more familiar term to the profession. Adair and Davis¹ felt that leukoplakia and kraurosis were symptoms or stages in one process and described the disease as atrophic dermatitis of the vulva. In the recent literature some writers cling to the more familiar term kraurosis, while others prefer the title leukoplakic vulvitis, and still others compromise on a combination of the two terms and write of leukokraurosis.

Much of the confusion surrounding this disease is due to the fact that its etiology is not definitely known. Adair and Davis, and Graves and Smith emphasize the importance of inflammation as an etiologic agent. Taussig³² believes that in some women, in or after the menopause, a special disturbance of ovarian secretions causes a complete disappearance of the elastic tissue in the upper layers of the skin of the vulva about the introitus. This leads to greater friability of the skin and minute breaks in its continuity through which bacteria gain entrance, producing a low grade inflammation. The resulting exudate causes pruritus. The trauma of rubbing or pressing produces more cracks and more infection, and the vicious circle progresses until changes of kraurosis have been produced.

There is considerable evidence that an ovarian dysfunction or cessation of ovarian hormonal activity is an important factor in the etiology of this condition. In the first place, it usually begins at or soon after the menopause. The average age of 121 reported cases was 53.4 years. In the second place, when it appears in younger women it is associated with evidences of ovarian dysfunction. In Goldberger's¹¹ series the youngest patient was 29, but she had never menstruated. One of Johnson's¹⁵ patients, age 33, had always menstruated.

* Read at the Fifty-second Annual Meeting of the Southern Surgical Association, Augusta, Ga., December 5, 6, 7, 1939.

very irregularly Taussig³² reported the case of a young woman, age 26. She began to suffer with pruritus at the age of 13, but her menstrual history was normal. He observes that possibly the explanation lies in the developmental abnormality localized about the skin of the vulva due primarily to alterations of the pituitary hormone. One of my cases was 29 years of age, but several years previously she had been subjected to a bilateral oophorectomy.

There are several questions that must be answered before one is justified in accepting the deficiency of ovarian hormone as the sole cause of the disease. Since every woman lacks ovarian hormone after the menopause, one would expect the disease to be the rule, not the exception, and yet Adair and Davis encountered leukoplakic vulvitis in only 23 instances among 9,682 gynecologic patients examined for the first time in the University of Chicago Clinic, an incidence of 0.24 per cent.

The second question that arises is why are the manifestations of the disease confined to the skin about the vulva and anus? Is there evidence that ovarian hormones have some peculiar effect on the skin of this region? Loeser²⁰ showed that during pregnancy hormones are deposited in the skin by means of the blood stream. He also calls attention to the fact that baboons have a menstrual cycle which is very similar to that of the human female. During the actual menstruation a slight swelling of the anal and vaginal zones becomes apparent. This swelling gradually increases during the following two weeks and culminates on the fourteenth day as a turgid edema. It is evident that this manifestation of estrus appearing in the genital skin is the result of activity of follicular hormone. Peters and Macbeth²³ believe that although the human female does not possess an external "sexual skin" highly sensitive to estrogenic stimuli as do certain apes, it does not follow that ovarian hormones have no effect on the morphology and vascularity of the skin of the vulva and the rest of the body. Cruickshank and Sharman⁷ believe that the deposition of glycogen in the vaginal epithelium is dependent upon ovarian activity. Lewis and Weinstein¹⁹ produced acidity of the vaginal secretions by the administration of estrin. Papanicolaou and Shorr²² found that treatment with ovarian hormone showed definite changes in the vaginal epithelium, and Foss¹⁰ contends that estrogen is necessary for the growth, development, and health of the genital skin, on which it has specific effect.

The conclusion to be drawn from the work of these and other observers is that normally ovarian hormone exerts some protective influence over the genital skin, and that in certain women the withdrawal of the hormone results in an inflammatory process with leukoplakia and kraurosis as its principal gross manifestation, and pruritus its chief symptom. Such a rationalization of the etiologic process may be logical, but it is certainly open to criticism. There must be other factors, as yet unknown, that are important etiologic agents in the production of this disease.

It has been the experience of most observers that the symptom that sends

most of these patients to a physician is a very severe and intractable pruritus. So intense is this pruritus that many of the patients are isolated from social contacts. To add to their misery, the associated excoriations and fissures become secondarily infected with burning, stinging, soreness, and dyspareunia. Graves and Smith found that in their series of kraurosis the symptoms complained of were, in order of frequency, burning on micturition, pruritus, pain and irritation of the vulva, vaginal discharge, burning of the vagina, and burning on defecation.

The physical findings are quite characteristic. Early in the disease the tissues about the clitoris, labia minora, inner margins of the labia majora, and at times the perianal skin, appear slightly edematous and dusky red in color (Jayle). As the disease progresses leukoplakic spots appear, and the skin becomes pale, thin and shining, and marked here and there with fissures and excoriations. Still later, the skin resembles parchment, thin and shrunken, and the labia minora are atrophic or obliterated entirely. Berkley and Bonney divided leukoplakia into four stages. First, reddening, swelling, excoriations, and dryness, second, retraction, thickening, and whitening of the tissues, third, fissures and ulcers with discharge and at times bleeding, fourth, complete involution, the skin surface is smooth, shiny, and white.

Taussig³³ believes there are two basic phases of the disease, the hypertrophic and the atrophic. In a progressive disease the histologic picture naturally changes as the disease advances. In the early stages there is thickening of the keratin layer with parakeratosis. The epithelial layer is wider than normal and the papillae are elongated (acanthosis). The eleidin layers appear very distinct. There is considerable hyperemia and round cell infiltration in the connective tissues. As the disease progresses the parakeratosis yields to a hyperkeratosis. The eleidin layer becomes dark, almost black at times, and the acanthosis disappears. The hyperkeratosis persists. The thickened epithelial layer gradually thins until in advanced cases the stratum germinativum may consist of a very narrow layer of cells. In the connective tissue the round cells appear in fairly well circumscribed areas, and there are marked collagenous changes. Taussig has stated that the late atrophic stage is not an abrupt change. There are gradations between it and the hyperplastic stage so that areas midway between the two are commonly found.

It is often difficult to differentiate leukoplakic vulvitis from numerous other conditions associated with pruritus. Elizabeth Hunt¹⁴ believes that many cases reported as leukoplakia are in reality lichen planus. Bonney³ describes two conditions, lepidosis vulvae and leukoderma vulvae, which are frequently confused with leukoplakia. Adair and Davis insist that all conditions which engender itching of the vulva, such as yeast or fungus infection, parasites, neurodermatitis and syphilis, must be ruled out. In a most enlightening article, Ketton and Ellis¹⁷ show the gross and histologic similarity between kraurosis vulvae and scleroderma circumscripta. They conclude that leukoplakia of the vulva is frequently superimposed on various pathologic processes whether primarily of a degenerative or inflammatory nature.

TABLE I

COLLECTED SERIES OF REPORTED CASES OF LEUKOPLAKIC VULVITIS SHOWING ITS RELATIONSHIP TO CARCINOMA

Author	Number of Cases Leukoplakic Vulvitis	Number of Cases Showing Malignancy Present
Taussig ³³	79	39
Goldberger ¹¹	8	2
Drant ⁹	5	3
Rigby ²⁶	4	4
	—	—
Totals	96	48 Malig 50%

Leukoplakic vulvitis is a disease of major importance because it is definitely a precancerous condition. A glance at Table I will show that in a series of cases of leukoplakic vulvitis reported by several authors, 50 per cent were malignant. On the other hand, if a large series of cases of carcinoma of the vulva are examined, above 30 per cent will be associated with, or arise from, a leukoplakic base. Rentschler²⁵ reviewed 71 cases of primary epithelioma of the vulva seen at the Mayo Clinic and found that 40 per cent gave a definite history of preexisting pruritus, but he was able to find leukoplakia in only five cases (Table II). Counsellor,⁶ in remarking on the extraordinarily low figure, observes that many of these cases had undergone previous treatment by procedures which unquestionably changed the histologic picture.

TABLE II

COLLECTED SERIES OF REPORTED CASES OF CARCINOMA OF THE VULVA SHOWING THE RELATIONSHIP OF CARCINOMA TO LEUKOPLAKIC VULVITIS

Author	Number of Cases Carcinoma of Vulva	Number of Cases Showing Leukoplakia
Taussig ³²	76	39
Hoffman ¹³	20	8
Kearns ¹⁶	17	4
Graves and Smith ¹⁷	21	16
Goldberger ¹¹	13	7
Rentschler ²⁵	71	5
	—	—
Totals	218	79 Arising in leuko 36%

Almost every conceivable form of therapy has been applied in the treatment of leukoplakic vulvitis. Local applications are totally inadequate. Roentgenotherapy as a method of treatment is contraindicated. Graves and Smith have seen evil results from roentgenotherapy and radium, and do not hesitate to condemn it. They believe that its use is illogical as radiation creates in the tissues a sclerotic retraction not unlike that of kraurosis. Taussig found that none of his cases treated by roentgenotherapy or radium showed more than temporary relief. Of the 23 cases reported by Adair and Davis,

16 were treated by roentgenotherapy by them or elsewhere, five received temporary relief, three were made worse, and eight received no benefit

Swift²⁹ found that a patient suffering with leukoplakia vaginitis had an achlohydria. Upon treating her with hydrochloric acid, the pruritus greatly improved and the white spots disappeared. Taking advantage of the work of Wolbach and Howe,³⁹ who found that guinea-pigs which had been fed on a diet deficient in vitamin A had vaginæ which usually contained accumulations of keratinized cells and frequently a thickened and shaggy epithelium, he began to treat a series of cases with hydrochloric acid and vitamin A in the form of cod liver oil. He was able to follow 41 of the 42 cases so treated, and he found that the irritation had been relieved in every instance.

Since leukoplakic vulvitis is distinctly a disease of, or after, the menopause, and since the younger cases are so definitely associated with some abnormal ovarian function, it would seem that a logical line of treatment would be to provide ovarian hormone in large doses. In the United States treatment by this method has been almost universally unsatisfactory.

In Goldberger's¹¹ 13 cases, female sex hormone or roentgenotherapy, or both, was administered in all but one case. In every instance, the results were poor. Adair and Davis treated three cases with amniotin. One showed improvement, one was made worse, and one was not affected. Taussig found that endocrine treatment, in the form of either hypodermic injections or ovarian, lutein or pituitary extracts, failed to produce any appreciable result.

In the British literature a number of mildly encouraging reports are found. Witherton and MacGregor³⁸ treated three patients with a mild degree of kraurosis vulvæ with 3 mg of stilbestrol (a synthetic estrogen) daily by mouth, and described their local and general condition as being considerably improved. Peters and Macbeth²³ treated a case by combined intravaginal and intramuscular ovarian therapy with marked improvement of the leukoplakia. Deanesly and Parkes⁸ showed that longer effect of the hormone could be attained by the implantation subcutaneously of tablets of the hormone. Foss treated 48 cases with injection of estradiol in large doses, vaginal suppositories, local application of an ointment containing estradiol, tablet implantation, hydrochloric acid, and vitamin A. He concludes that very few patients received complete and lasting comfort. He feels that the application of an ointment containing follicular hormone is of benefit in the treatment and will often relieve the pruritus temporarily.

Wilson³⁷ noted improvement of the leukoplakia and the pruritus in five cases he treated with injections of alcohol. Mueller,²¹ Usher and Campbell,³⁵ Leamonth, Montgomery and Counsellor¹⁸ advocate the relief of the severe pruritus by resection of the sensory nerves of the perineum.

Surgery is perhaps the choice of methods of treatment. It is necessary to resect the entire area involved, which may require the removal of the clitoris, perianal skin, the labia minora, and most of the labia majora. The wisdom of this procedure is twofold. (1) It successfully relieves the distressing symptoms, and (2) it eradicates the precancerous condition. If the disease is ex-

tensive, necessitating a wide resection of the perineal and particularly the perianal skin, there are two areas where closure may be difficult. First, the triangular area of skin between the lower margin of the vagina and the anus, and second, the approximation of the skin to the anal mucosa. The former difficulty has been remedied by Taussig, who forms a flap of the posterior vaginal wall, which, when properly mobilized, can be drawn over the perineal body down to the anterior margin of the anal mucosa where it is anchored with silk sutures (Fig 1). Cattell⁵ turns a pedicle-flap from the buttocks into the perineal space, suturing it to the vaginal mucosa and to the mucosa of the rectum (Fig 2). When it is necessary to resect the perianal skin,

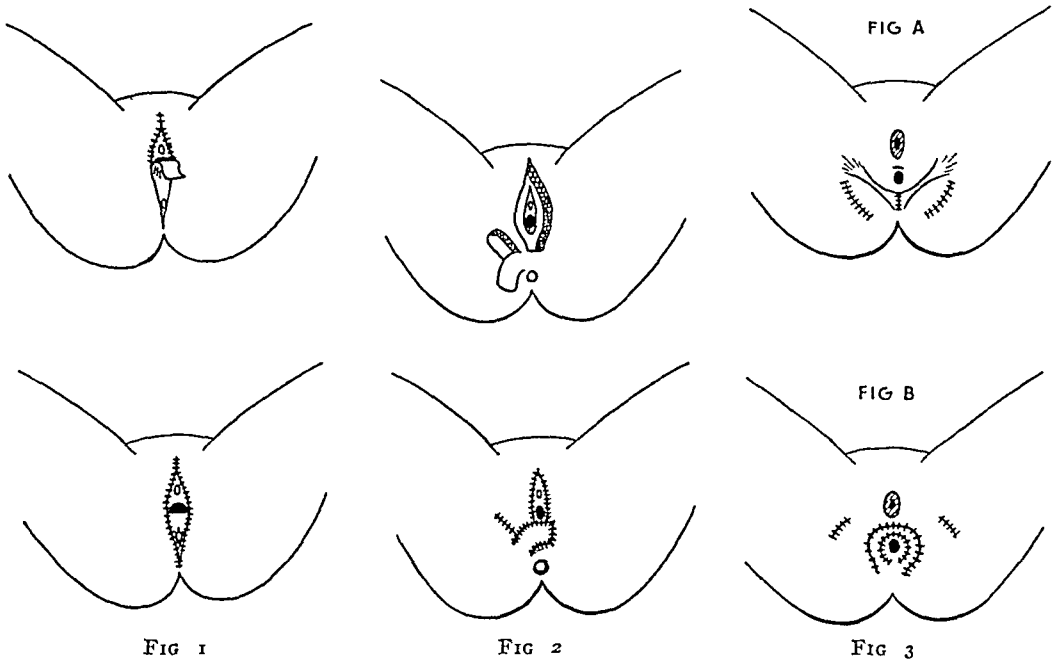


FIG 1—Taussig's method of closing the denuded area between the vagina and rectum. A flap of the posterior vaginal wall is pulled over the perineal body and sewed to the anal mucosa.
FIG 2—Cattell's method of closing the denuded area between the vagina and anus. A pedicle flap from the buttock is sewed over the perineal body.
FIG 3—The author's method of lessening tension on the anal mucosa after removal of the perianal skin. A tube pedicle graft from the buttock is utilized.

the anal mucosa must be pulled out under considerable tension in order to suture it to the skin. This often leaves a very unsatisfactory condition about the rectum. Taussig obviates this difficulty by leaving intact a bridge of anal skin on either side of the anus. In one of my²⁸ cases in which there was extensive perianal scarring, the tension was relieved by removing the scar and grafting the skin of the buttocks over the denuded area by using a tube-pedicle-graft on either side (Fig 3).

In the series I wish to report there are six cases, two of which have been previously reported.²⁷ A detailed analysis of these cases will be found in Table III. The average age for the group was 52. Pruritus, pain, and soreness from excoriations were the chief complaints in every case. The clinical diagnosis in each was leukoplakic vulvitis, and in every instance a vulvectomy was performed. The first case was operated upon seven years ago, the most recent, one year ago. All have remained under constant observation. In

TABLE III

DETAILED ANALYSIS OF SIX CASES OF LEUKOPLAKIC VULVITIS

Case No	Color	Age	Previous Menstrual History	Symptom	Clinical Diagnosis	Treatment	Pathologic Diagnosis	Onset	Complications +
1 R C	W	58 yrs	Menopause at 45	Pruritus	Leukoplakic vulvitis	Vulvectomy, 1932	Leukoplakia	1933	Pruritus, fissures, abundant culture of a yeast
2 W S	W	29 yrs	Bilateral oophorectomy	Pruritus Ulcers	Leukoplakic vulvitis	Vulvectomy, 1932, 2nd operation 1933	(a) Leukoplakia, (b) scleroderma morpha	1935	Scars about rectum, ulcers and fissures
3 S B	N	49 yrs	Menopause at 39	Pruritus Dyspareunia	Leukoplakic vulvitis	Vulvectomy, 1935	Leukoplakia	1938	Complete loss of pigment in zone about anus, no plaques
4 J McC	W	46 yrs	Beginning menopause	Pruritus	Leukoplakic vulvitis	Vulvectomy, 1936	Leukoplakia	1937	Pruritus, dusky red zone about vagina and anus
5 M J	W	64 yrs	Menopause at 51	Pruritus	Leukoplakic vulvitis	Vulvectomy, 1936	Leukoplakia		None
6 M F	W	66 yrs	Menopause at 44	Pruritus Burning pains	Leukoplakic vulvitis	Partial vulvectomy, 1938, complete vulvectomy, 1939	Intra-epithelial epithelioma	1939	Return of symptoms and recurrence

* The complications in Cases Nos 1, 2, 3, and 4 were treated with an ointment containing estradiol, as suggested by Foss.¹⁰ The appearance of the skin improved and the pruritus was temporarily relieved in Cases Nos 1, 2, and 4. After one month, Case No 4 showed pigmented areas in the white zone about the anus.

two cases, Nos 2 and 6, the process continued to spread, necessitating a second operation. In Case No 2 the histologic picture was confusing. The condition was diagnosed by one pathologist as leukoplakic vulvitis. A second pathologist diagnosed the condition as scleroderma morphea. In accord with the reports of Ketion and Ellis, it is likely that both processes were present. An intra-epithelial epithelioma was found in one case, an incidence of malignancy for the series of about 17 per cent.

It is interesting to note that there was some complication in every case.



FIG 4—Case 3 Leukoplakic vulvitis (hypertrophic stage). This condition is said to be rare in the Negro race.

save one. This is most discouraging in the light of the almost uniformly excellent results quoted in the literature.

In Case No 1 there was complete relief for almost two years. Thereafter there appeared a reddish discoloration of the skin about the vagina and rectum and, intermittently, a return of pruritus. A culture showed an abundant growth of a yeast, and it has been very difficult to control the pruritus.

In Case No 2, after the second operation, the rectal mucosa was greatly stretched and ulcers appeared in the scar. A pedicle tube-graft relieved some of the pull on the rectal mucosa. The grafted skin has remained in excellent condition for four years. Ulcers have continued to form in the scar tissue.

along the edges of the graft and between the folds of the buttocks. Numerous cultures have been made. On one a diphtheroid organism was found, on others, *Staphylococcus aureus* and *Staphylococcus albus*. No yeast or fungi have been found. These ulcers heal readily under treatment with silver nitrate but soon reappear.

Case No. 3 is the only one in the series which occurred in the Negro



FIG 5—Case 3. Microscopic picture from case illustrated in Figure 1. There is present hyperkeratosis, widening of the epithelial layer, and acanthosis.

(Fig. 4) The microscopic picture of the tissue removed in this case is illustrated in Figure 5. A successful vulvectomy was performed (Fig. 6). Two years after operation, there was complete loss of pigment of the skin about the rectum (Fig. 7). There were no subjective symptoms. The histologic picture of a biopsy made over this area showed hyperkeratosis and absent rete pegs, and in the corium there were fibrosis, collagenous changes and lymphocytic infiltration. The basal pigment layer stopped abruptly at the border of the lesion (Fig. 8).

In Case No. 4 the pruritus returned, one year after operation. A dusky zone appeared on the skin about the rectum and vagina about 2 cm. in width. At times this skin was covered with fine scales. At other times it appeared glazed and parchment-like. There were no fissures or leukoplakic plaques. Cultures were negative for yeast or fungi. A biopsy showed, chiefly, hyalinization of the corium, atrophy of the rete, and some dyskeratosis.

In Case No. 5 there were no complications.

In Case No 6 there was a definite return of the epithelioma. A second operation was performed. Union was perfect, but it has been too recent to state whether or not a cure will result. It probably would have been wiser to have performed a Bassett³⁴ type of operation upon this patient.



FIG 6—Case 3 Postoperative results following a vulvectomy

The postoperative complications in four of the cases were treated by applications of an ointment suggested by Foss. This contained estrogenic substance, 1,800 rat units per gram, and 15 mg of crystals A-estradiol (Sheering Corporation). It was hoped that ovarian substance applied to the skin might have some local effect on the skin. The pruritus in Cases Nos 1 and 4 was temporarily relieved. The ulcers in Case No 2 disappeared in part, but in areas of tension, as posterior to the rectum, they continued to appear at intervals. The white area about the rectum in Case No 3 showed pigmented spots, about the size of the end of a match, after one month's use of the ointment. The treatment has been too recent to determine whether or not this was due to the treatment or purely incidental.



FIG 7—Case 3 Complete loss of pigment of the perineal skin, two years after vulvectomy



FIG 8—Case 3 Section made at the junction of the pigmented and nonpigmented areas. Except for loss of pigment, a slight increase in the amount of keratin, and beginning collagenous changes in the corium, there is little difference between the pigmented and nonpigmented areas.

CONCLUSIONS

(1) Leukoplakic vulvitis, an inflammatory condition of the perivaginal and perianal skin, occurs at, or after, the menopause, or in association with evidences of ovarian hypofunction. It is a precancerous condition.

(2) Its etiology is not known. It is probable that an ovarian hormone exerts some protective influence over the genital skin, and that the withdrawal of hormone results in inflammation, leukoplakia and kraurosis. There must be some other etiologic factors involved which are still unknown.

(3) It is likely that other conditions are frequently confused with, or associated with, leukoplakic vulvitis.

(4) Vulvectomy is the treatment of choice since it gives symptomatic relief and eradicates a precancerous condition.

(5) Six cases of leukoplakic vulvitis are reported in detail. In all save one there were postoperative complications.

(6) An ointment containing estradiol was found to be of benefit in relieving pruritus which had recurred as a postoperative complication. The benefits obtained warrant further use of this ointment.

BIBLIOGRAPHY

- ¹ Adair, F L, and Davis, M E. Chronic Atrophic Dermatitis of the Vulva. *Surg, Gynec and Obstet*, **61**, 433, 1935.
- ² Berkley, C, and Bonney, V. Kraurosis Vulvae. *Proc Roy Soc Med*, **3**, 29, 1909-1910.
- ³ Bonney, V. Leukoplakic Vulvitis and the Conditions Liable to Be Confused with It. *Proc Roy Soc Med*, **31**, 1057, 1937-1938.
- ⁴ Breisky. Quoted by Graves and Smith¹².
- ⁵ Cattell, R B. Kraurosis Vulvae. *Surg Clin North Amer*, **14**, 1279, 1934.
- ⁶ Counsellor, V S. Leukoplakic Vulvitis. *Minnesota Med*, **14**, 312, 1931.
- ⁷ Cruickshank, Robert, and Sharman, Albert. The Biology of the Vagina in the Human Subject. *Jour Obst and Gynec, Brit Emp*, **41**, 369, 1934.
- ⁸ Deanesly, R, and Parkes, A S. Further Experiments on the Administration of Hormones by the Subcutaneous Implantation of Tablets. *Lancet*, **235**, No 2, 606, 1938.
- ⁹ Drant, Patricia. Early Diagnosis of Precancerous Vulvar Lesions. *Med Rec*, **147**, 377, 1938.
- ¹⁰ Foss, G L. Further Developments in the Treatment of Kraurosis, Leukoplakia and Pruritus Vulvae. *Jour Obst and Gynec, Brit Emp*, **46**, 271, April, 1939.
- ¹¹ Goldberger, M A. Kraurosis Vulvae, with Report of Thirteen Cases. *Am Jour Obst and Gynec*, **25**, 58, 1933.
- ¹² Graves, W P, and Smith, G V S. Kraurosis Vulvae. *JAMA*, **92**, 1244, 1929.
- ¹³ Hoffman, P E. Malignancies of the Vulva. *Am Jour Obst and Gynec*, **33**, 60, 1937.
- ¹⁴ Hunt, Elizabeth. Discussion of report of Peters and Macbeth²³. *Proc Roy Soc Med*, **30**, 1330, 1937.
- ¹⁵ Johnson, George. Kraurosis Vulvae. *Am Jour Obst and Gynec*, **26**, 110, 1933.
- ¹⁶ Kearns, P J. The Comparative Tendency of Kraurosis and Leukoplakia of the Vulva to Become Malignant. *Canad M A J*, **33**, 48, 1935.
- ¹⁷ Ketron, L W, and Ellis, F A. Kraurosis Vulvae (Leukoplakia) and Scleroderma Circumscripta. *Surg, Gynec and Obstet*, **61**, 635, 1935.

- ¹⁸ Learmonth, J R, Montgomery, H, and Counsellor, V S Resection of Sensory Nerves of Perineum in Certain Irritative Conditions of the External Genitalia Arch Surg, 26, 50, 1933
- ¹⁹ Lewis, R M, and Weinstein, L The Production of Vaginal Acidity by Estrin Surg, Gynec and Obstet, 63, 640, 1936
- ²⁰ Loeser, Alfred A Resorption and Action of Follicular Hormone Rubbed into the Skin Jour Obst and Gynec, Brit Emp, 44, 710, 1937
- ²¹ Mueller, S C Leukoplakia Vulvitis Proc Staff Meet, Mayo Clinic, 6, 5, 1931
- ²² Papanicolaou, G N, and Shorr, Ephraim Action of Ovarian Follicular Hormone in the Menopause as Indicated by Vaginal Smears Am Jour Obst and Gynec, 31, 806, 1936
- ²³ Peters, A D K, and Macbeth, A N Partial Resolution of Leukoplakia Vulvae under Estrin Therapy Proc Roy Soc Med, 30, 1330, 1937
- ²⁴ Reder, Francis Kraurosis Vulvae and Inguinal Adenitis of a Malignant Nature Surg, Gynec and Obstet, 33, 554, 1921
- ²⁵ Rentschler, C B Primary Epithelioma of the Vulva, an Analysis of Seventy-one Cases ANNALS OF SURGERY, 89, 709, 1929
- ²⁶ Rigby, O C Treatment of Cancer and Precancerous Lesions of the Vulva New Orleans Med and Surg Jour, 90, 445, 1938
- ²⁷ Sparrow, T D Kraurosis Vulvae Southern Surg, 3, 117, 1934
- ²⁸ Sparrow, T D The Viability of the Tube-Pedicle Skin Graft Am Jour Surg, 41, 92, July, 1938
- ²⁹ Swift, B H Achlorhydria as an Etiologic Factor in Pruritus Vulvae, Associated with Kraurosis or Leukoplakia Jour Obst and Gynec, Brit Emp, 43, 1053, 1936
- ³⁰ Szasz Quoted by Adair and Davis ¹
- ³¹ Taussig, F J Contribution to the Pathology of Vulvar Disease Am Jour Obst and Gynec, 6, 407, 1923
- ³² Taussig, F J Leukoplakic Vulvitis and Cancer of the Vulva Am Jour Obst and Gynec, 18, 472, 1929
- ³³ Taussig, F J Leukoplakia and Cancer of the Vulva Arch Dermat and Syph, 21, 432, 1930
- ³⁴ Taussig, F J Late Results in the Treatment of Leukoplakic Vulvitis and Cancer of the Vulva Am Jour Obst and Gynec, 31, 746, 1936
- ³⁵ Usher, B, and Campbell, A D Kraurosis Leukoplakia and Pruritus Vulvae Treatment by Resection of the Sensory Nerves of the Perineum Canad M A J, 38, 432, 1938
- ³⁶ Weir, R F Quoted by Graves and Smith ¹²
- ³⁷ Wilson, W M Pruritus Vulvae, Chronic Vulvitis and Leukoplakic Vulvitis Treatment by Alcohol Injection Northwest Med, 33, 268, 1934
- ³⁸ Witherton, W R, and MacGregor, T N Clinical Observations with Stilbestiol Brit Med Jour, 1, 10, 1939
- ³⁹ Wolbach, S B, and Howe, P R Vitamin A Deficiency in the Guinea-Pig Arch Path and Lab Med, 5, 239, 1928

URETERAL TRANSPLANTATION*

WILLIAM E. LOWER, M.D.

CLEVELAND, OHIO

ORDINARILY, in adults, we prefer to perform this operation under spinal anesthesia. The patient is put in a rather extreme Trendelenburg position so that the abdominal viscera are well out of the pelvis. Formerly, we transplanted the right ureter first and in about ten days or two weeks, the left ureter was transplanted. Latterly, we have been doing more and more cases in a single sitting, transplanting both ureters during a single operation. The risk of peritonitis, which we formerly feared, we no longer consider as being likely to occur. Patients are prepared the same as those who have an operation upon the rectum or colon, namely, three or four days of saline cathartics and daily irrigations of the bowel, opiates the day before operation, and during this entire time, a nonresidue diet.

The ureter is easily exposed, particularly on the right side, just beneath the peritoneum, and about two and one-half inches of the lower end of the ureter is freed and divided and the lower end ligated with fine catgut. The retroperitoneal space is then closed, being especially careful that no oozing occurs. The point in the bowel in which transplantation is made depends entirely upon where the ureter seems to fit best and with least angulation, sometimes, we use the white line and in all cases, cut through the bowel to the mucous membrane. One point, which we believe has made the operation much easier, is to begin transplanting the ureter at its proximal end (Fig. 1). Included in the needle and suture, we pick up a little of the adventitious tissue along the ureter (Fig. 2), this is to prevent it from shifting its position. As a rule, we do not fix the bowel to the parietal peritoneum, believing that a certain amount of flexibility is less liable to cause stricture than immobility. Nearly always, the danger point for stricture is where we first start the implantation into the intestine. At this point, by dividing the trough on each side down to the mucous membrane, there is less danger of this occurring (Fig. 3).

With an intravenous pyelogram, it is very easy to determine the condition of the ureters before undertaking the operation. In very large, wide ureters, the problem becomes a more difficult one.

As to the age at which these operations should be undertaken, we have again changed our position and now will undertake them any time after three months of age, we have quite a series of children under one year of age. They do very well and we believe cause less disturbance and after care, and the

* Illustrated by moving pictures of the procedures when presented before the Fifty-second Annual Meeting of the Southern Surgical Association, Augusta, Ga., December 5, 6, 7, 1939.

URETERAL TRANSPLANTATION

child is given just one training for sphincter control. This refers largely, of course, to cases of exstrophy of the bladder.

In cases of malignancy after the ureters have been transplanted and are functioning, we remove the bladder extraperitoneally by dividing the urethra and pulling it well up into the wound and then dissecting it free from the peritoneum and surrounding tissue. A large rubber and gauze pack is placed in the cavity.

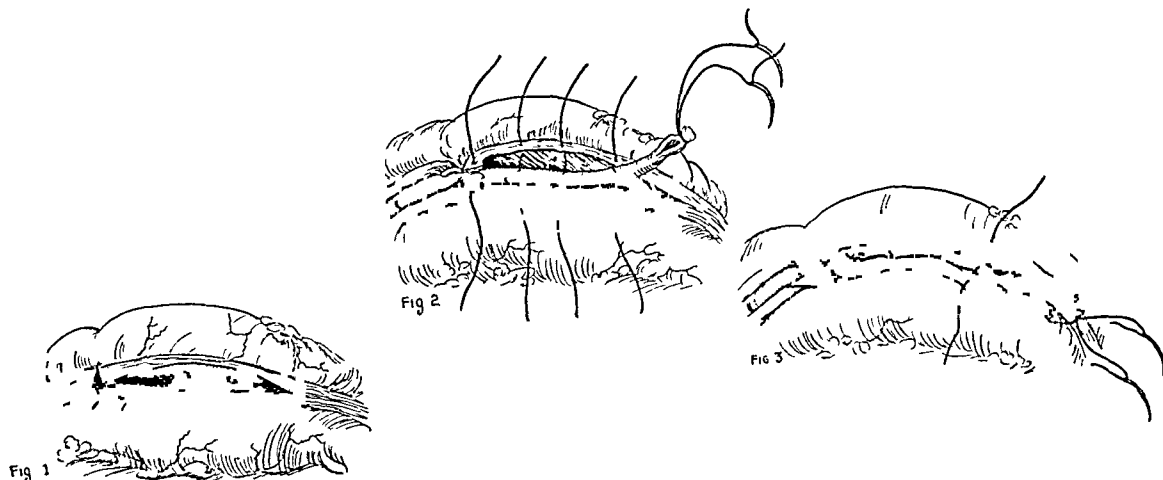


FIG 1—Showing division of the tense tissue on each side of trough

FIG 2—Bringing cut ends together to relieve tension on ureter

FIG 3—Showing position of ureter after transplant

We now have a total of 108 cases in which ureteral transplantation has been performed, and have some patients who have gone for more than 20 years, and who are getting along comfortably.

CONCLUSIONS

There can be no doubt that patients with these distressing congenital anomalies can have their social status restored and live a comfortable existence.

In the malignant tumors of the bladder, if they are seen early enough, we believe that total cystectomy and ureteral transplantation offers an opportunity for possible cure and certainly great relief from vesical distress.

DISCUSSION—DR ADDISON G. BRENIZER, Charlotte, N. C. I think one of the greatest advantages we have in surgery is that we are individuals, and I suppose that, from the standpoint of those who do not live with us in the South, they might suspect us of most any romance.

In performing the Ferguson-Higgins-Brenizer transplantation of the ureters, we lay both ureters in the submucosal position and cover them with muscularis and serosa. Before closing over these layers, we put No. 1 nasal wire in a loop over the ureter on both sides and leave them for ten days. The wire-ends are out the rectum through catheter. The greatest advantage is that any bruising, any bleeding and edema subside and the ureters continue to run to the bladder. There are no obstructions to the ureter, as Doctor Douglass and his group found at Vanderbilt, because the bowel movements pulled on the wire and dragged it down. We pass the two ends of this wire through a small whistle-tip catheter and it straddles the ureter, and then we bend it into a slit in the catheter. The whole catheter and wire, looped over the ureter, may be moved up and down together or the wire alone moved up and

down in the catheter. We do assure the free position and movement of the wire and catheter and thus are acquainted with the fact that the wire-loop over the ureter is not obstructing it.

The diagrammatic sketches (shown on the screen) show a stretch of ureter and rectum. The serosa and muscularis are incised down to the mucosa. This incision is ample in length and dissected to either side so as to amply and easily, cover the ureter when placed in it. About 18 inches of a No. 1 tonsil wire is cut obliquely at its ends, bent in the form of a hairpin and with one end on each side of the ureter as it lies on the mucosa, the ends are pushed down through the mucosa into the lumen and out the rectum. Thus the hairpin wire straddles the ureter and remains with a loop above around the ureter, the ends emerging below from the catheter and the catheter in turn from the anus.

When both ureters are loosely healed in the bowel and all bleeding, exudate and edema have subsided, that is, in about ten days, first one ureter and then the other is cut by drawing down on the wire so as to compress the ureter with the loop above, and applying a very high electro-cutting current to the wire ends where they emerge from the catheter and anus below. It is better to use two small whistle-tipped catheters, one for each ureter, and cut the two ureters on different days, proving, by employing intravenous urography, that the ureters are emptying into the rectum and that the bladder or bladder field is dry. With no urine to the bladder, it is more easily and aseptically removed. One of the greatest advantages of this operation is that after severing and emptying the whole proximal ureter into the rectum, the distal ends, attached to the bladder, may be disregarded and not tucked back into the bowel, and the bladder so much more easily removed. Added to this, the dry bladder and better asepsis, bleeding may be controlled by central ligations within the abdomen. Then the bladder does not have to be removed in fistula, incompetent sphincter, etc. In exstrophies, the removal of the mucosa and plication of the bladder before covering with muscle and skin is sufficient.

Our latest improvement, in certain cases of ureteral transplantation, is to loop the wire over the ureter, pass an end of the hairpin wire in and out of the mucosa, both ends of the wire through a No. 8 ureteral catheter, which catheter, in turn, is made to tunnel for an inch to an inch and one-half between the muscularis and mucosa, to emerge from the muscularis and come to the body surface through a stab-hole in the side. The ureter is severed in the same way as when the catheter emerges from the anus. This latter operation has the advantage of a more complete asepsis, but the disadvantage of the greater difficulty in tunneling between muscularis and mucosa.

DR. HENRY L. DOUGLASS, Nashville, Tenn. I enjoyed Doctor Lower's excellent demonstration of the technic he employs in uretero-intestinal anastomosis. Except for minor differences in procedure I employ the same operation. I wish to discuss, briefly, certain technical points which lessen the operative risk.

First of all, the position of the ureter within the bowel wall must be maintained by suture until union has occurred between these structures. To that end Doctor Lower, in closing the muscle layer of the bowel wall over the ureter, includes the external coat of the latter in each suture. During this step it is important that the suture does not penetrate the lumen of the ureter for, if that happens, a urinary fistula may result and especially so if the transfixing stitch is under tension. He pointed out that some of the adjacent connective tissue should be left attached to the dissected ureter. This is a very important point because it enables the operator to include this coat of adventi-

trous tissue rather than the wall of the ureter in the suture and this minimizes the possibility of damage to the lumen of the ureter. On the other hand, the proper relationship between the anastomosed structure will be maintained if the end of the ureter can be drawn well within the lumen of the bowel without tension and anchored there to the bowel wall by a chromic catgut suture. The muscle layer of the bowel wall can then be simply approximated over the ureter with a running catgut suture. This suture line should be protected by a second row of interrupted chromic catgut sutures. Finally, I think it is of value to rotate the sigmoid sufficiently to place the anastomosis in apposition with the incision in the posterior layer of the peritoneum where it is fastened by interrupted sutures. With union between the sigmoid and the posterior parietal peritoneum the anastomosis becomes retroperitoneal in line with the ureter and the bowel becomes fixed in its new relationship. This avoids the danger of peristalsis or distention pulling away the bowel and creating tension on the anastomosis.

At the completion of the anastomosis a fenestrated colon tube, which has already been introduced into the rectum, is adjusted so that its upper end is slightly above the union between the ureter and bowel. It is left in place to prevent a dangerous distention of the bowel in the area of the anastomosis.

Postoperative distention of the bowel may pull apart the edges of the wound in the intestinal musculature. The mucous membrane of the bowel then herniates through the wound carrying with it the ureter. The valve effect of the anastomosis is lost and the ureter becomes merely adherent to the bowel wall for a short distance before it directly enters its lumen. The systemic effect of this accident may not be immediately apparent. Later, however, these patients suffer from an ascending pyelonephritis which eventually destroys the kidney. Most of the upper urinary tract complications following ureteral transplantation are due to a faulty anastomosis.

We have used Bienizer's technic in operations upon dogs. The wires, looped over the ureters with their free ends coiled in the rectum, obstructed the ureters, and within ten days or two weeks caused considerable renal damage. It is impossible to obviate this obstruction so long as one operates upon dogs. In man, however, the ureters may be catheterized prior to operation. The catheters should remain in place to maintain free drainage of the upper urinary tract until the time arrives to remove the wires. Ureteral obstruction due to the encircling wire can thus be avoided in man.

DR W. L. PEPLE, Richmond, Va. I would like to report three cases of ureteral implantation performed in St. Luke's Hospital, two by Dr. Stuart McGuire, and one I reported in 1929, which I did myself. These cases illustrate how long this operation is effective.

CASE REPORTS

Case 1—J. B., came with a history of exstrophy of the bladder at the age of four, in 1919. His ureters were implanted into the sigmoid in two stages. Since then he has had one or two moderately severe attacks of pyelitis, but last year made his M. A. degree, as a fine looking, outstanding young man, in perfect health.

Case 2—F. B., came with exstrophy of the bladder at the age of six, in 1917. The bladder was excised, and the ureters, with small buttons of bladder tissue around them, were transplanted into the sigmoid in one stage. He came back with pyelonephritis and renal calculi in 1928, and died, having lived 11 years following surgery.

Case 3—The case of Mrs. C. was reported before the Southern Surgical Association, in 1929. She presented herself, in the year 1927, with irreparable bladder injury. Three months prior to admission, she underwent an extremely difficult delivery. The

child was born dead, and she was torn well up into the rectum. She developed a severe infection, and there followed a sloughing of the floor of the bladder which included the entire urethra. Then a hemiplegia developed, paralyzing the right arm and leg.

We first repaired the perineum and restored the sphincter muscle, then allowed her to go home for six months. When she returned we first transplanted the right ureter, and a week later the left, by the method of Doctor Coffey. When the abdomen was opened, we removed the appendix and tied and divided tubes so that another pregnancy would not occur and pelvic infection would be eliminated. She made an uninterrupted recovery and I have seen her from time-to-time during the past 12 years. The last visit I give verbatim from my notes:

"June 19, 1939. I had a visit this morning from Mrs. C., and her husband. She states that she is in good health and that the leg and foot have become almost normal. She has a little spastic contraction in the right hand and right biceps and the muscles of the arm are rather tense and spastic. This is all that remains of her hemiplegia.

"She has had absolutely no trouble in the control of her urine and goes as long as most women, and never has an accident. She has had several mild attacks of pyelitis but by eating and drinking carefully and by prompt treatment, these have given rise to no trouble.

"Mr. and Mrs. C. have adopted a little girl. She is about five years old and extremely attractive. This couple is deeply grateful and very happy. I do not know when I have had a visit that gave me more pleasure."

DR. FRANCIS R. HAGNER, Washington, D. C.: I enjoyed Doctor Lower's paper, and the simplicity of the operation appeals to me very much. We know how often patients who have carcinoma of the bladder have large ureters. We have employed the Coffey technic on these patients. I wonder if bringing a catheter out of the rectum may not add an element of safety to the operation when this condition is present. We have had one patient, with a ureter as large as an ordinary finger, who was operated upon by this method with an excellent result. He is still alive after nine years, and able to hold the urine in his rectum for nine hours. I have talked to my friends about one man who suffered terribly after operation. Every time he passed urine from the rectum he screamed with pain. He lived about a week and at autopsy we could find nothing that would account for the pain.

DR. WILLIAM E. LOWER, Cleveland, Ohio (closing): I am sorry the picture conveyed the idea that we, at any time, included the ureter in our needle. All we include is the adventitious tissue, this is done to keep the ureter from sliding back. We begin at the proximal end and place our sutures to about one inch from the end, and then the opening is made into the intestine, and the end of the ureter is drawn in by double-threaded catgut sutures.

As to the question of fixing the intestine, we have tried both ways and think they do just as well if a certain amount of flexibility is allowed. In very large ureters it may be well to use a catheter.

The only things we claim for this technic are its simplicity, and the fact it can be undertaken at one stage. We do put a rectal tube in for several days for drainage of urine and irrigate this rather regularly with saline solution. I believe we shall be performing more of the bilateral transplantations at one sitting.

LEG AMPUTATIONS IN DIABETIC GANGRENE

SAUL S. SAMUELS, M.D.

NEW YORK, N. Y.

FROM THE FOURTH SURGICAL DIVISION, BEVELLUE HOSPITAL, NEW YORK, N. Y., DR. CARL G. BURDICK, DIRECTOR

ALTHOUGH great strides have been made in the conservative treatment of diabetic gangrene,^{1 2} particularly in those cases where infection plays a major rôle, there are still a certain number of cases which, in spite of conservative measures, require amputation as a life saving measure.

There are two major indications for amputation in diabetic gangrene, the more common being rapid spread of the gangrenous process with no signs of healing or of the formation of a line of demarcation. Such cases usually have a zero oscillometric index at the ankle level. Another indication for amputation is uncontrollable infection of the foot. Such cases, again, are usually associated with extremely inadequate arterial circulation in the extremity as evidenced by a zero oscillometric index.

Previous teachings were to the effect that diabetic gangrene, particularly with infection of the foot, is of such a nature that infection would spread throughout the body or into the thigh if an amputation were performed without taking adequate precautions against such spread. These precautions consisted of either leaving the stump wide open at the time of operation or of inserting drains into the partially sutured stump or of leaving untied sutures in place which could be removed at a moment's notice or be tied sometime after the operation if no infection or gangrene of the stump were evident. These precautions were based upon the erroneous assumption that diabetic gangrene with infection of the foot presupposed the extension of the infection throughout the entire extremity, particularly in the lymphatics, hence, cutting across infected lymphatics was sure to carry the infection into the thigh tissues and thus produce secondary infection of the stump.

The mortality from this type of operation was extremely high, in some hospitals up to 75 per cent. Those cases that survived the operation required prolonged stay in bed with subsequent development of bed sores, pneumonia and other complications of prolonged bed rest. Healing of stumps, particularly those that were left open, was a matter of months requiring skin traction, secondary operations and in some cases skin grafts to cover the denuded area. In other words, an amputation for diabetic gangrene was a formidable procedure attended with great risk and with a high mortality.

Recent experiences, pioneered by Eliason and Wright,³ and McKittrick⁴ have demonstrated the fallacy of previous conceptions of amputation in diabetic gangrene and have demonstrated, conclusively, that in this field a mountain has been made out of a molehill. Increasing experiences have proven that an amputation for diabetic gangrene, even in the presence of

severe infection, is a simple procedure attended with a low mortality if the operation is performed as simply as possible and the proper postoperative care is carried out

Preoperative treatment in these cases must be simplified. In other words, transfusions and intravenous injections of glucose and saline with insulin coverage are not necessary except where there is definite evidence of dehydration. If the patient cannot be made sugar-free before the operation by large doses of insulin, it is an indication of the fact that undrained infection is present in the foot. This being the case, it is a waste of time to try to render the patient sugar-free or to reduce his blood sugar if such infection is present. Unnecessary delay in the operation because of this fact may prove disastrous. In such a case immediate removal of the infected area is indicated regardless of the diabetic status.

The choice of an anesthetic is very important. We have found cyclopropane to be the best in these cases for the following reasons. It requires a large concentration of oxygen in its administration and renders sufficient anesthesia with no bad after-effects. Where cyclopropane is not available, nitrous oxide gas may also be used with satisfactory results. As no very great relaxation is required for the operation, ether is unnecessary and may be harmful. Because of the very slight shock and the beneficial stimulating effects of cyclopropane, I can see no reason for the use of spinal anesthesia in these cases. On the other hand, the use of spinal anesthesia in these patients, who are usually elderly and arteriosclerotic, is attended with considerable danger and may cause thrombosis of the main arteries of the opposite extremity.

There are certain technical points in the performance of the operation which must be rigidly adhered to if primary union and an uneventful recovery are to be attained.

Because of the damage that may be caused by even the momentary use of compression, no tourniquet is used. The amount of blood lost without the use of a tourniquet is negligible, providing care is used in careful clamping and tying of every vessel as it is cut.

Preparation of the operative field is very important and requires close attention to detail. As a rule, the operative area is prepared by the nurse on the ward in the usual manner. With the patient in position on the operating table, secondary preparation of the operative field must be carried out. This consists of thorough cleansing with benzine applied by means of sterile gauze or a sterile towel, followed by additional cleansing with alcohol applied in the same manner. The area may now be painted with iodine in the usual manner.

Proper draping is also essential. While the leg is elevated a large sheet is drawn over the lower half of the table in such a fashion that it reaches below the patient's buttocks and completely covers the edge of the table. A sterile towel is now draped around the upper third of the thigh and fastened with a towel clip. A half sheet is now placed on the table in such a fashion that the leg may be lowered into it and the sheet then draped around the

lower portion of the leg so as to completely enclose the nonoperative area in a sort of boot. A sterile bandage is the best means of enclosing the leg in the sterile sheet so that the boot is formed. Another sheet is now used to drape the upper portion of the body and additional towels may be placed above and below the immediate operative field. In fastening the various sheets and towels with clips, it is necessary to be sure that the leg may be raised from the table at any time during the operation without danger of contamination.

In line with the policy of simplification of procedure, in order to minimize handling of tissues and unnecessary dissection, a simple circular incision is used, avoiding the formation of flaps of any kind. The level of the skin incision need be no higher than the upper border of the patella. The old idea that one must amputate as high as possible in diabetic gangrene in order to get above the level of infection or into an area of better circulation has proven

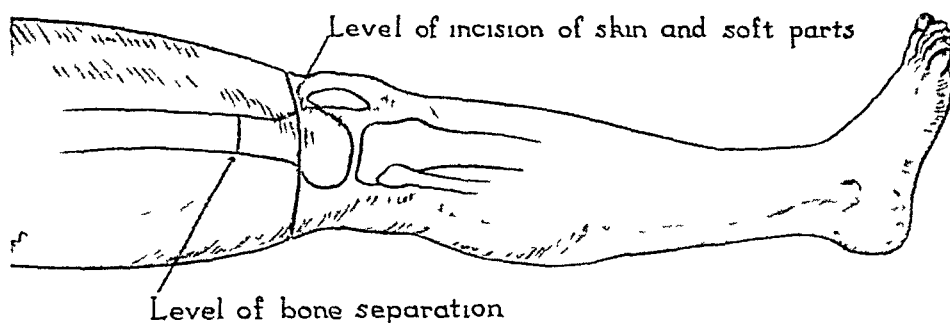


FIG 1—Supracondylar amputation for diabetic gangrene

to be entirely fallacious. As pointed out previously, the infection is almost always confined to the foot and even in the presence of lymphangitis no fear of infection of the thigh may be entertained. Another reason for the low incision is the conservation of the thigh muscles and of a good length of femur both of which are necessary for the proper use of an artificial limb. It is now generally admitted that the lower third of the thigh offers the best possible location of the amputation for the subsequent use of an artificial limb, hence, the traditional operation known as "midthigh" amputation should be abandoned in diabetic gangrene. The proper terminology is "supracondylar" amputation (Fig 1). The skin incision should be made with a medium sized scalpel which should be discarded after the skin is penetrated and a fresh scalpel used for the soft parts. In this type of operation, where precise technic is necessary, the use of a clumsy amputation knife is out of the question. All vessels are clamped as they are cut and particular care must be taken so that accurate hemostasis is obtained before the bone is cut through. This obviates the necessity of later searching for bleeders which only adds to the trauma of the operation.

At this low level of amputation, the popliteal artery is usually found, without difficulty, in the posterior tissues rather close to the bone. The sciatic nerve is not injected with alcohol nor is any particular attention paid

to it other than to be sure that it is cut with one clean stroke. No difficulty has been encountered with the nerve by this method.

It is important that the soft tissues be cut in one plane and that no attempt be made to undermine skin or fascia or to dissect into the tissue for any reason whatsoever. When the femur is reached and the soft tissues are completely severed, a towel moistened with warm saline is applied to the proximal tissues and by gentle traction the soft tissues are pulled back, exposing the femur for about two inches proximal to the level of skin incision. The periosteum is incised at this level and scraped distally (Fig 2). The bone is then sawed through at the same level and the wet towel is now removed.

A clean operative field is necessary at all times and the extravagant use

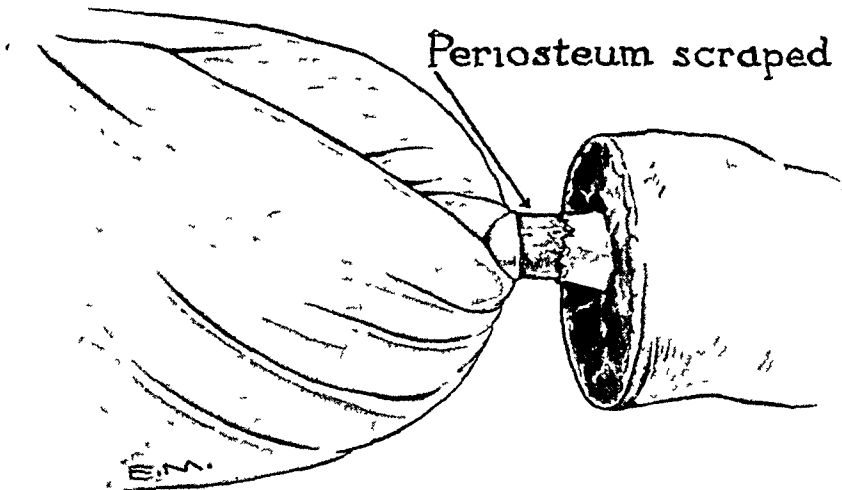


FIG 2—Level of bone separation

of towels is recommended. After each stage of the operation, the operative field should be completely recovered with fresh towels. Ligation of all vessels is now effected. Previously, plain catgut was used for ligatures but at the suggestion of Doctor Burdick, fine silk was substituted. Although the use of silk for ligatures entails additional care and accuracy in tying, the results from its use are highly gratifying, inasmuch as there is practically no reaction in the stump from the use of silk as contrasted to the usual postoperative temperature, edema and slight inflammatory reaction resulting from the use of catgut. The last nine cases operated upon with the use of silk have healed perfectly with no reaction. Fine silk is also used for tying the popliteal artery.

When the bone is severed, it will be noted that the soft tissues fall together, anteroposteriorly, with no tension whatsoever over the end of the bone. To maintain the tissues in a good position and to avoid the formation of dead space, a few fine silk sutures are used to proximate the muscles and fascia (Fig 3). The skin is approximated very carefully with either fine silk or silkworm gut, extreme care being taken, as in a thyroid or hernia operation that no inversion of skin takes place.

Dressings are now applied to the stump in such a way that not too much

bulk is produced. There is no necessity for the use of splints or other methods of immobilizing the stump. A snug bandage is applied and the entire dressing held in place with a few strips of adhesive plaster. On returning from the operating room, the stump is elevated to an angle of 45° by means of a pillow. It is kept this way for about two days.

A great advantage of the operation performed in this manner is that the patient may get out of bed on the following day and may be in a wheel-chair every day thereafter. This is very important in these cases because most of these patients are elderly and are prone to develop bed sores and pneumonia if kept in bed for any length of time. It is advantageous for the diabetic condition, also, if these patients are able to be out of bed so soon after the operation.

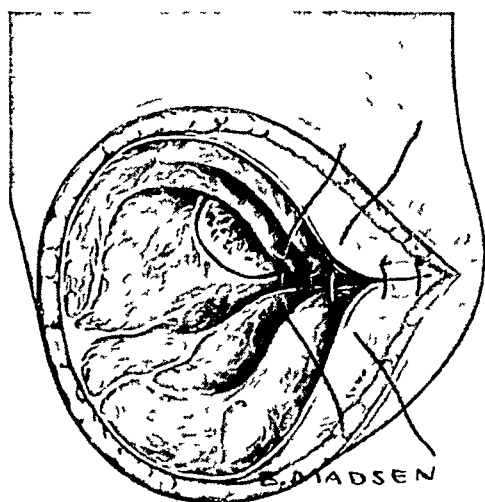


FIG 3—Method of closure with silk sutures
No drainage is used



FIG 4—Appearance of stump eight days
after operation

The stump may be redressed after 48 hours and every other day thereafter. A simple, light, dry dressing is sufficient. On the sixth or seventh day the sutures may be removed (Fig 4) and the skin edges held in place by means of strips of sterile adhesive plaster. In some instances, the patient may be allowed on crutches after the first week or even sooner. Most patients are discharged from the hospital from the seventh to the tenth day and are instructed not to consider themselves bed patients when arriving home but to sit up in a chair all day and start the use of crutches. It is remarkable to observe the recuperating powers of even the oldest patients who have undergone this simple amputation after a siege of pain and general weakness induced by the loss of sleep.

No special changes are necessary in the postoperative care of diabetics. As a rule, the day after the operation patients are put back on their regular preoperative diet with the usual amount of insulin. However, where unusually large doses of insulin were necessary before the operation in an infected case, care must be observed in the dosage to avoid insulin shock after the infected foot has been removed. In other words, such patients usually require much less insulin after the operation than before. No hesitation need be felt in

increasing the diet as long as proper coverage with insulin is maintained. Of 33 amputations performed personally at Bellevue Hospital and in private practice by the above method, three died, a mortality of 9 per cent. One of these cases had hypertension and severe nephritis, of which he died a few days after the operation. Another, who was a poor risk, developed bronchial pneumonia and died within 48 hours. A third, who persisted in breaking his diet after the operation, developed a severe infection of the stump and left the hospital against advice. Follow-up indicated that this patient died subsequently but the manner of death is not known. All other cases in this series healed by primary union with the exception of a very few instances of superficial collection of seropurulent material in a few cases where catgut had been used for ligatures. The last nine cases, in which silk was used instead of catgut, showed no postoperative reaction of any kind in the stumps and perfect primary union was obtained in all. The clean reaction-free stumps, obtained with the use of silk, are a revelation to the surgeon who is accustomed to other methods of amputation for diabetic gangrene.

Since amputation for diabetic gangrene is usually a life saving procedure, one is justified in performing the operation above the knee as here described. There may be an occasional case, very rare, however, in which amputation below the knee may be attempted. As a requisite for such an amputation an oscillometric reading of 10 or more must be obtained at the ankle level. If such a low amputation is attempted in a case with a poor oscillometric index, healing, if it occurs at all, will be delayed for an indefinite time usually necessitating a second amputation above the knee. As mentioned previously, the occasion for a low amputation will be rare because where the circulation is adequate, infection, if present in the foot, can be controlled according to newer methods of treatment, and gangrene, if present, will usually demarcate very definitely, requiring no major amputation.

If an amputation below the knee is to be performed, a modification of the supracondylar amputation may be performed as follows. A circular incision is made about eight inches below the lower border of the patella. The incision is continued in the same plane through the soft tissues down to the bones. In order to convert the limb at this point into a single bone condition as in the higher amputation, a longitudinal incision is made over the lateral surface of the fibula at right angles with the circular incision proximally along the line of the fibula for about three inches. At the upper level of this lateral incision, the fibula is severed by means of a Gigli saw and the lower end of the fibula is severed in the same manner. The piece of fibula is now removed and the soft tissues are retracted with a wet towel as in the thigh amputation. The tibia is severed about one inch lower than the fibula and the sharp anterior edge of the tibia is carefully beveled with either a saw or a large rongeur. The soft tissues are now brought from behind forward and sewed over the end of the tibia to the under surface of the skin. The skin edges are approximated carefully and no drainage is used. Here again silk should be used and the same postoperative procedure as in the thigh amputation is carried out.

Two operations performed by this technic resulted in primary union. One patient developed a coronary artery thrombosis and died suddenly seven days after the operation.

The objections to amputation below the knee are the increased trauma necessary in the complicated dissection and the poor protection to the end of the stump because of the small amount of soft parts available for coverage.

CONCLUSIONS

Traditional fear of the outcome of amputation in diabetic gangrene is no longer justified.

By means of simplified technic, decreased operative shock and changed post-operative care, amputation for diabetic gangrene can be considered a relatively minor procedure.

With the newer method of amputation, the operative mortality of diabetic gangrene can be greatly reduced.

REFERENCES

- ¹Samuels, S. S. Fundamental Principles in the Treatment of Diabetic Gangrene. *Surgery*, **2**, 225, August, 1937.
- ²Samuels, S. S. The Diagnosis and Treatment of Diseases of the Peripheral Arteries. New York and London, Oxford University Press, 1936.
- ³Eliason, E. L., and Wright, V. W. Diabetic and Arteriosclerotic Gangrene of the Lower Extremities. *Surg., Gynec. and Obstet.*, **42**, 753, 1926.
- ⁴McKittrick, L. S., and Root, H. F. Diabetic Surgery. Philadelphia, Lea and Febiger, 1928.

THE INFLUENCE OF SUTURES UPON OPERATIVE WOUNDS*

JOSEPH E BELLAS, M D

PEORIA, ILL

FOR MANY YEARS, the medical profession has traditionally assumed that the ideal buried suture material had to be absorbable. Out of this assumption has grown the popularity which catgut has enjoyed in the past. For almost as many years surgeons have, on the other hand, been lamenting the many disadvantages of catgut, but because of its excellent physical characteristics and ease of handling and because no satisfactory substitute has been devised to replace it, many surgeons have continued its use in spite of its defects. In many instances, other surgeons have turned away from catgut and have resorted to the use of silk^{1 2 3} as buried sutures. Some of the disadvantages of catgut were thus eliminated only to be replaced by other disadvantages almost as disagreeable. Thus for many years the pendulum has swung from catgut to silk and from silk to catgut, but in spite of new processes in the manufacture of each type of suture, the undesirable effects remained.

What are the disadvantages of these sutures? Clinically, it has been generally observed by surgeons that in many apparently clean surgical cases where catgut was used, fluid collections and even abscesses arose in the incisions during the convalescence, the origin of which could not be accounted for. Many things were blamed for this occurrence—imperfect scrubbing of the hands of surgeons, assistants and scrub nurses, faulty aseptic technic resulting in contamination, imperfect sterilization of instruments and of the surgical linen. But when all these factors were thoroughly checked and corrected, edema and effusion of fluid in the incision still persisted. It was then thought that contamination of catgut with bacteria and spores was the underlying factor, and this probably with some justice^{4 5}. Methods of manufacture have, however, been devised whereby all contamination can be definitely overcome with a resultant sterile suture, but still the edema, drainage and unexplainable infections took place.

In the use of silk *in clean cases*, there was no great incidence of edema or noteworthy effusions but it was observed that, in a notable number of cases, some small points in the incision failed to heal, or, where primary healing apparently did occur, that draining sinuses developed later on which absolutely refused to heal until the offending suture was cut down upon and removed^{6 7}.

We strongly support the contention^{8 9} that the basis of these reactions with catgut and similar sutures rests on the fact that they are composed of animal material and hence act as reacting foreign bodies in the tissues. These sutures act as reacting foreign bodies because they are variably susceptible to

* Read before the Western Surgical Association, Omaha, Nebraska, December 3, 1938
Submitted for publication March 21, 1939

enzymatic action and the various chemiophysologic processes such as occur in the body. With silk this is less marked, but almost every surgeon who has used silk has observed the deteriorated appearance of a silk suture that has had to be removed.¹⁰ The qualities of these sutures and especially those of catgut are seriously disturbed by such contact until the catgut is completely dissolved or "absorbed" and silk definitely frayed. The claim of "absorbability" is, in essence, an admission of defection in a suture because of the above-mentioned influences to which it is liable. As a result of this reaction, the formation of edema or of actual collection of free fluid develops in the tissues. It is not difficult to understand that little repair can take place while this reaction is going on. It is not surprising, therefore, that with catgut, the strength of the incision is at its weakest about seven days after insertion. This has been confirmed by numerous investigators.^{11 12 13 14} The suture has become profoundly deteriorated or "absorbed" and no longer lends its strength to the incision. Noteworthy healing does not take place until after the reaction to the reacting suture is spent. It follows, then, that incisions heal not because of, but in spite of catgut.

A reacting animal suture may have another disadvantage—the products of its solution, disintegration or digestion may, when absorbed, induce allergic reaction.^{8, 15 16} We have personally conducted a few tests to demonstrate that true allergic reaction to catgut is no myth but a very definite phenomenon in some protein-sensitive individuals. It is also well known that the products of the disintegration of catgut are splendid culture media for bacteria and that an infection is actually aided and abetted by the presence of catgut.

In an effort to get away from sutures of animal origin, surgeons have used linen, and in the past few years have followed the example of Babcock¹⁷ and Kurlander¹⁸ in the use of soft annealed steel alloy wire as a superficial and as a buried suture. Linen, and in this I include Pagenstecher, has proved unsatisfactory because its capillarity allowed the absorption and retention of tissue juices which, by stagnation, became an excellent culture medium for bacterial growth. The not infrequent end-results were the formation of persistent draining sinuses much as with the use of silk.

The use of steel wire gave splendid results from the standpoint of absence of reaction and of favorable primary healing. But there were mechanical disadvantages in the matter of handling that proved very irritating during operations, and there was always the threat of medicolegal complications because of its radiopacity. Although steel wire fulfilled the requirements from the standpoint of nonreactibility and prompt repair of operative wounds, it was by no means the ideal suture for general use. Out of our own experiences at the Collins Clinic with varied sutures, coupled with those of others,¹⁹ arose the idea of formulating the qualities that an ideal suture should have. These are

(1) The suture should be sterilizable by common hospital and office methods, that is, by autoclaving and by boiling, without significant loss of desirable properties.

(2) The suture should possess pliability, satisfactory tensile strength, knot-holding qualities and uniformity for given sizes

(3) The suture should be nonreacting or relatively nonreacting in the body tissues

(4) It should be insusceptible to the action of tryptic enzymes in the body tissues

(5) It should be insusceptible to the chemical and physiologic agents in the body tissues

(6) It should be unaffected by bacteria and incapable of promoting the growth of bacteria

(7) It should be incapable of retarding the process of repair

(8) It should be incapable of inducing disturbing edema or of inducing effusions of tissue fluids in operative wounds

(9) It should be incapable of inducing allergic reaction and incidentally of toxic or carcinogenic influences

(10) It should be practically unaffected by clinical ranges of heat and moisture

(11) It should be *truly* noncapillary

(12) It should permit of ease in handling, at least equal to that of catgut

(13) It should be radiolucent

The logical conclusion that arises from the above requirements leads to

(14) The necessity of the suture being nonabsorbable

This is rather a tall order even for an ideal suture. We believe we have approached the desired result, and present, herewith, a new suture as an improved substitute for catgut and current sutures.

This new suture* is composed of incorporated synthetic plastic materials especially selected so as to meet the above requirements. These plastic materials are polymerized condensation products of aliphatic and aromatic alcohols with aliphatic aldehydes. Its appearance is very similar to that of catgut and it is prepared in equivalent sizes, but from that point on the similarity ceases.

We have used this new suture in some 300 cases of all descriptions, under all manner of conditions, and with varied technics. We have learned a lot of things about sutures in carrying out this work, and particularly in relation to the use of this suture. At first our sutures were crude and of a large size. We frequently used the equivalent of No. 2 double as a continuous suture, both in clean and in infected wounds. In 217 clean cases, seven developed localized reactions from mechanical irritation and some of these required a secondary procedure to remove the cause of the irritation.

These figures require further clarification in relation to changing technic (Table I).

It is obvious that the latter technic, as shown in Table I, has eliminated mechanical irritation almost to the point of extinction in clean cases, and has materially reduced stitch troubles in infected or contaminated cases. We are convinced that this mechanical irritation arises from sutures of large bulk and

* For convenience and simplicity, the name *plastigut* has been adopted for this suture.

INFLUENCE OF SUTURES



FIG 1—Shows a chromic catgut suture at the end of five days. The catgut suture is beginning to be absorbed with an inflammatory reaction, especially at the site of absorption

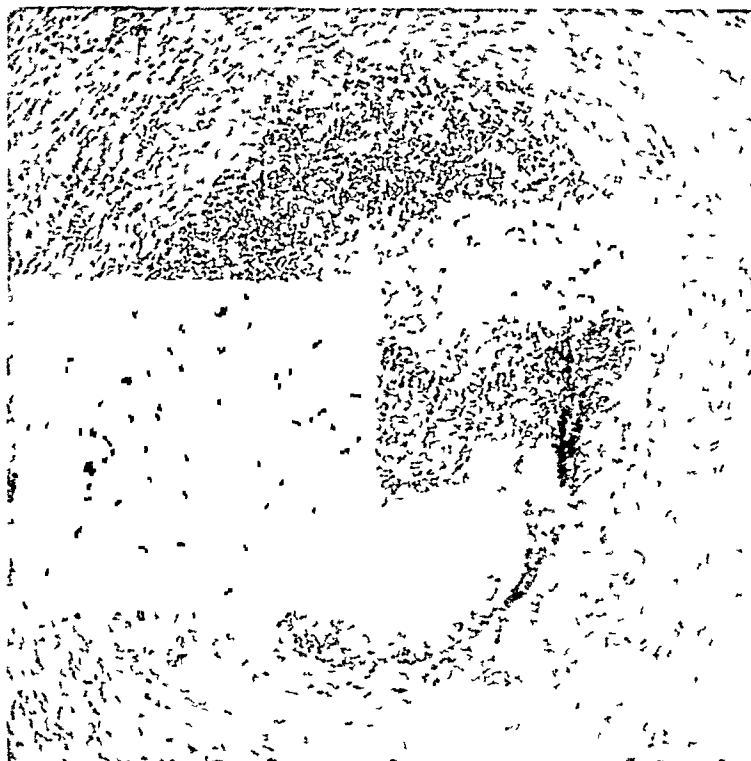


FIG 2—Shows a section at two weeks, in which a plain catgut suture is almost completely digested and replaced by a wide rounded area filled with acute inflammatory cells and showing central necrosis. This is virtually an acute abscess. Figures 1 and 2 are typical of the reactions with catgut

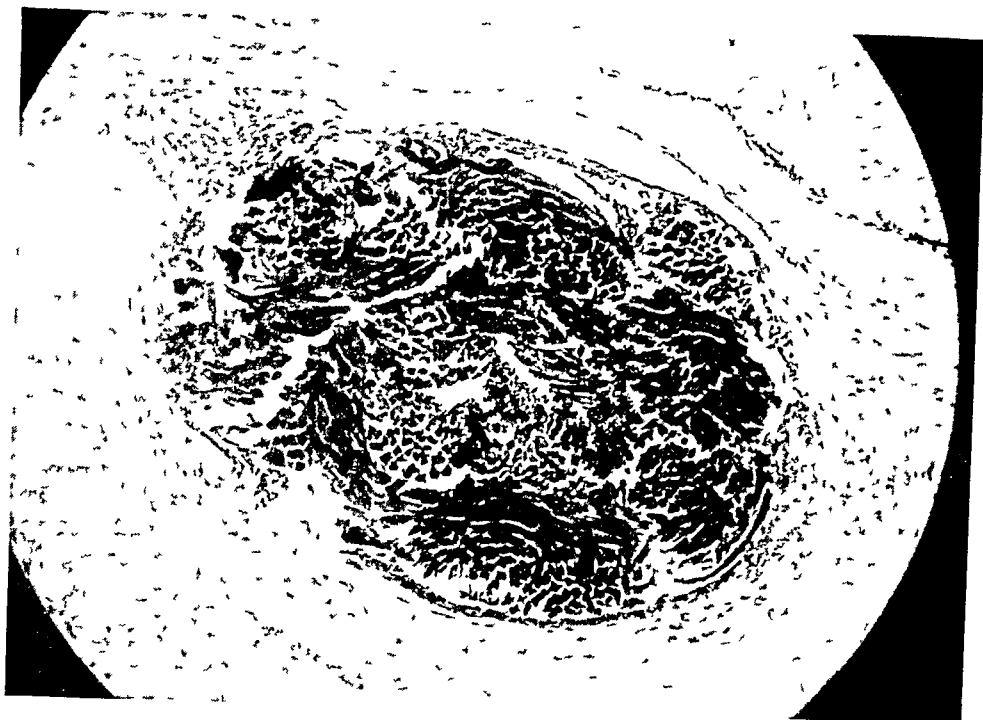


FIG 4—This is a section at four weeks of another type of silk suture claiming to be serum proof and noncapillary. Note the presence of inflammatory cells within the structure of the suture and between the fibers.



FIG 3—This is a typical section of a silk suture claiming to be noncapillary and serum proof. At seven days, a marked infiltration of inflammatory cells and serum can be seen between the fibers of silk. This shows very definitely how capillarity favors the retention and promotion of infection.

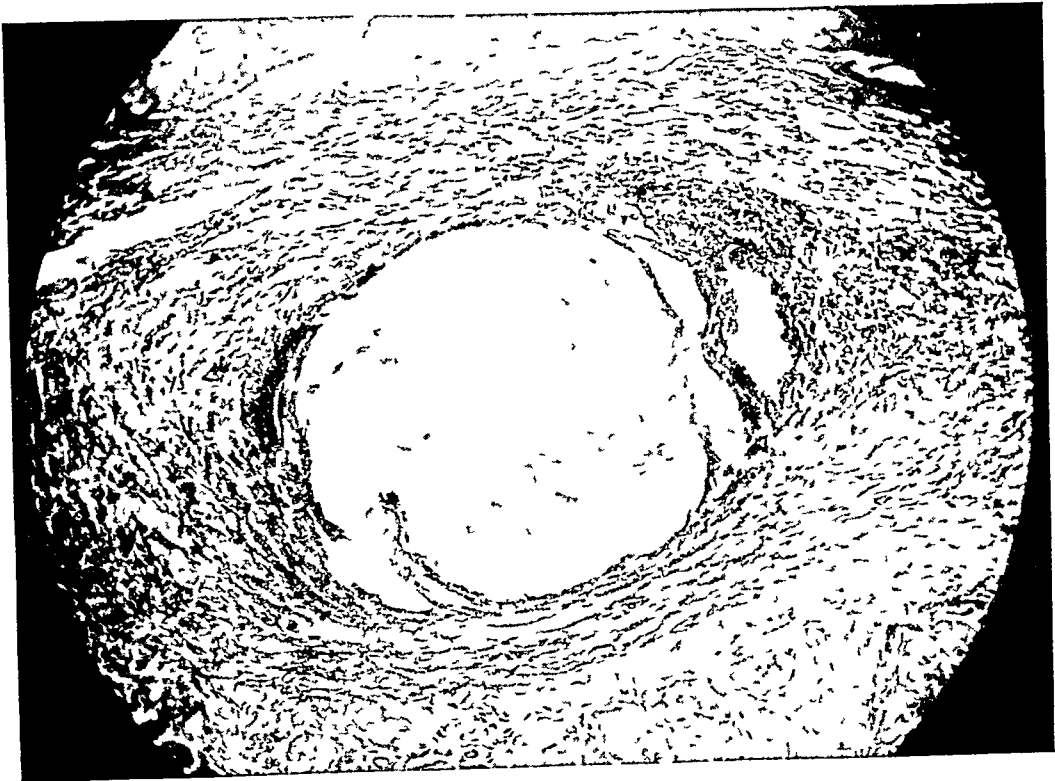


FIG 6—Section of plastic suture at two weeks. No reaction, no inflammation, no capillary

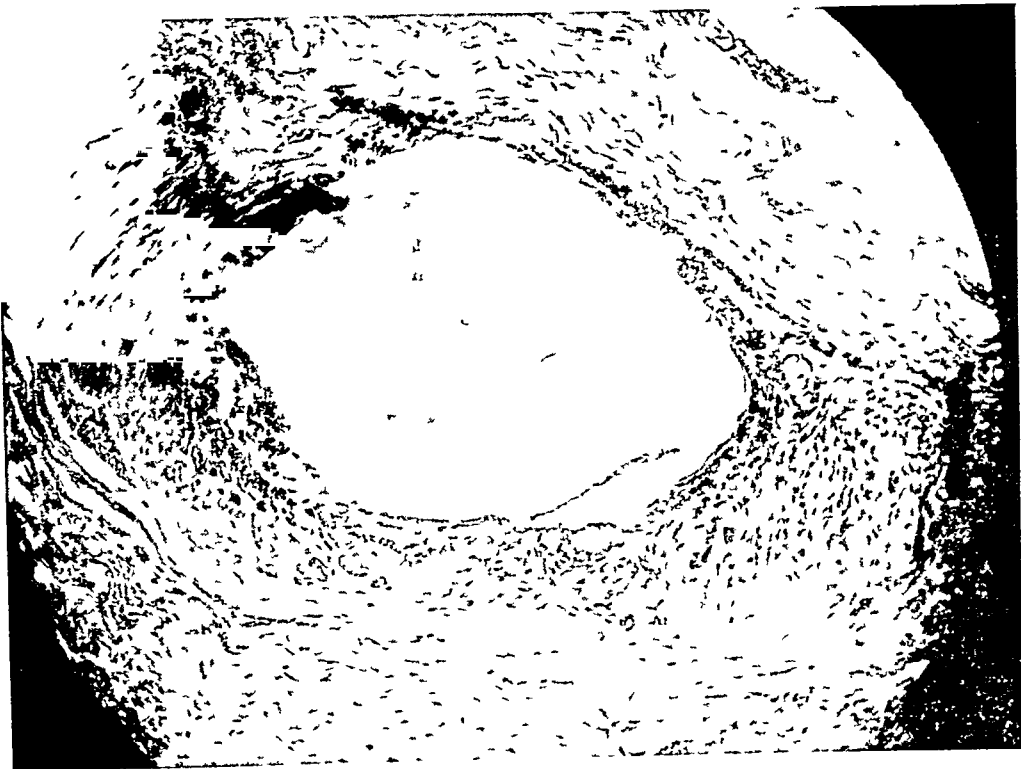


FIG 5—Section of plastic suture at seven days showing the suture surrounded by normal tissue with no evidence of inflammation in or around the suture

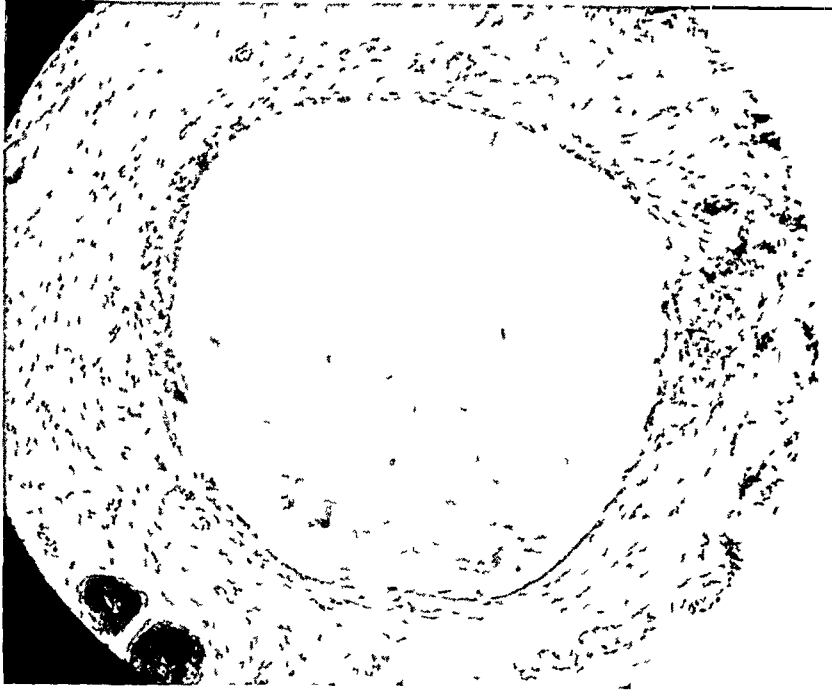


FIG 8.—Section of plastic suture at six months. No reaction, no inflammation, no capillarity—thus demonstrating quite definitely that it remains a nonreacting suture that causes no disturbance of the surrounding normal tissue.

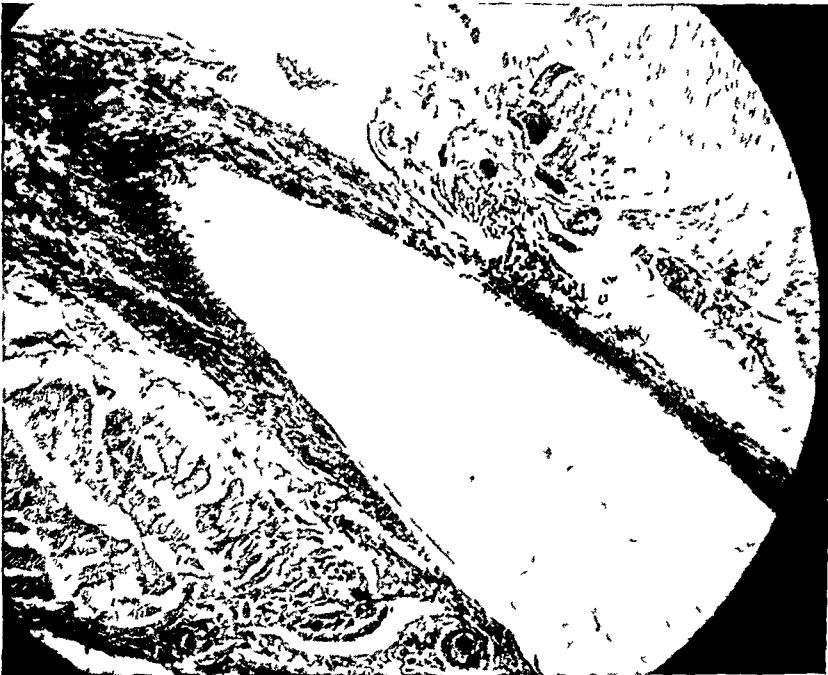


FIG 7.—Section of plastic suture at six weeks, after exposure to an infected field. The guinea pig chewed off its skin suture and the incision had to be resutured with wire the next day. The infection which resulted has now subsided and the suture has healed in. In spite of the marked infection around the suture there has been no tendency whatever for inflammatory invasion into the suture. There is no capillarity here.

from large knots. All others healed by first intention and have apparently remained so. Since we have adopted single threads and smaller sizes up to size No. 0, whether continuous or interrupted, healing has been primary in all but one case.

TABLE I

	C	S	Per Cent of S	I	S	Per Cent of S
1937 Group						
Continuous No. 2 plastic suture, double or single	105	6	5.7	21	10	47.6
1938 Group						
Continuous or interrupted No. 0000 to No. 0 plastic suture, single	112	1	0.875	23	4	17.0

Code: C = Clean cases; S = Stitch or sinus trouble; I = Infected or contaminated cases.

In a two-year experience with this suture, we have encountered about all the complications that are possible with the suture. We have studiously tried to analyze our experiences and are now convinced that a certain technic should accompany its use. We are impressed by one observation. That continuous sutures within the peritoneal cavity can be used with impunity. We have had no intraperitoneal complications following the use of the continuous suture in either clean or infected cases. There are no objections, however, to the use of interrupted intraperitoneal sutures. In clean cases, extraperitoneal sutures may be continuous or interrupted. Generally speaking, interrupted sutures are preferable. It has been a matter of great satisfaction to see how promptly incisions healed by primary intention, with no evidence of reaction, and to note the pliability of the skin and underlying tissues during the healing period. In infected and in drained cases, interrupted suture technic is compulsory for extraperitoneal locations. We are convinced that the advocates of the Halsted silk technic will now find an almost ideal material in this new suture. In infected cases, there is a definite tendency for the infection to localize without the spreading infection we so frequently observed with catgut. The interrupted loops of this suture will become loosened when uprooted by a slough and in most cases will be cast off with the slough. Occasionally it may be necessary to use a hook for a loop that has become loosened but not cast off. Those sutures which have become buried in viable tissues remain buried and cause no trouble.

We are convinced that no sizes above No. 0 or at most No. 1 should be used, and that all strands should be used single. The most useful range of sizes in our work has been between Nos. 00000 to 00. The strands are tough, have a substantial "feel" equal to that of catgut and superior to the limpness of fine silk. Those who are advocates of the Halsted silk technic will find an improved substitute in a relatively heavier, relatively stronger, nonreacting, nonabsorbable suture that has all the advantages of silk without its disadvantages.

Although we have performed experimental work upon guinea-pigs and to a less extent on dogs, our convictions arise chiefly on the basis of clinical application and results

The photomicrographs show a series of typical sections of various sutures at different periods (Figs 1 to 8)

SUMMARY

No contribution in the suture field will occur unless we reorganize our ideas about sutures. A new principle is offered which distinguishes between reacting and nonreacting foreign bodies. Catgut, silk and sutures of animal origin are of protein composition and as such act as reacting foreign bodies more or less intensely. They are also subject to numerous chemiophysiologic, bacteriologic and physical influences, the total effect of which is to hinder and delay primary repair in operative wounds. The ideal suture must be one that is nonreacting, one that is not affected by the enzymatic, chemical, physiologic, bacteriologic and physical influences with prompt, normal repair. Such an accomplishment is believed to have been attained in a new plastic suture on the basis of extensive animal and clinical experience.

Since this article has been submitted for publication, a larger number of cases have been analyzed as of October, 1939

REVISED TABLE

<i>First Series</i>	C	S	Per Cent of S	I	S	Per Cent of S
Continuous No 2 plastigut, double or single	105	6	5.7	21	10	47.6
<i>Second Series</i>						
Continuous or interrupted No 0000 to No 0 plastigut, single	230	1	0.435	50	9	18.00
Code C = clean cases S = stitch or sinus trouble I = infected or contaminated cases						

The author is indebted to Dr. Andrew C. Ivy, Professor of Physiology at Northwestern University, for his outline of animal experiments and for his encouragement throughout the period of this study.

REFERENCES

- Halsted, Wm. Stewart. Ligature and Suture Material. J A M A, 60, 1119, April 12, 1913.
- Whipple, A. O. The Use of Silk in the Repair of Clean Wounds. ANNALS OF SURGERY, 98, 662-671, 1933.
- Allen, J. C. Bell. The Fetish of Catgut. Med Jour Australia, 2, 150-151, 1934.
- Meleney, F. L., and Chatfield, M. How Can We Insure Sterility of Catgut? Surg, Gynec and Obstet, 50, 271-277, 1930.
- Clock, R. O. Bacterial Species Found in Nonsterile Surgical Catgut Sutures. Surg, Gynec and Obstet, 66, 878-881, 1938.
- Starlinger, F. The Later Fate and the Clinical Effect of Silk Threads in the Wall of Gastro-Intestinal Fistulae. Zentralbl f Chir, 54, 2562-2566, 1937.
- Gatch, W. D. Some Considerations on Wound Healing. Southern Surg, 7, 505-516, 1938.

- ⁸ Babcock, W Wayne Catgut Allergy, With a Note on the Use of Alloy Steel Wire for Sutures and Ligatures *Am Jour Surg*, 27, 67-70, 1935
- ⁹ Reil, Hermann The Catgut Problem *Chirurg*, 4, 17-23, 1932
- ¹⁰ Donaldson, J K, and Cameron, Richard R Study of Use of Silk, Catgut and the Noble Plication with Reference to Abdominal Adhesions *Surgery*, 5, 511-521, 1939
- ¹¹ Kraissl, C J, and Meleney, F L A Method for Determining the Time of Catgut Digestion in Vitro *Surg, Gynec and Obstet*, 59, 161, 1934
- ¹² Howes, E L, and Harvey, S C Strength of Healing Wound in Relation to Holding Strength of Catgut Suture *New England Med Jour*, 200, 1235, 1939
- ¹³ Jenkins, H P Clinical Study of Catgut in Relation to Abdominal Wound Disruption *Surg, Gynec and Obstet*, 64, 648-662, 1937
- ¹⁴ Rhoads, J E, Hottenstein, H F, and Hudson, I F Decline in Strength of Catgut after Exposure to Living Tissues *Arch Surg*, 34, 377-397, 1937
- ¹⁵ Hinton, J W Allergy as an Explanation of Dehiscence of Wound and Incisional Hernia *Arch Surg*, 33, 197-209, 1936
- ¹⁶ Kraissl, C J, Kesten, B M, and Cimmiotti, J G Relation of Catgut Sensitivity to Wound Healing *Surg, Gynec and Obstet*, 66, 628-635, 1938
- ¹⁷ Babcock, W Wayne Ligatures and Sutures of Alloy Steel Wire *J A M A*, 102, 1756, 1934
- ¹⁸ Kurlander, Joseph J Rustless Steel Wire—A New Addition to the Surgeon's Armamentarium *Jour Bone and Joint Surg*, 12, 191, 1930
- ¹⁹ Rau, O Experiences with the Modern Suture Material "Medrafil" *Zentralbl f Chir*, 64, 509, 1937

FRACTURE OF THE CAPITELLUM*

REPORT OF A CASE SUCCESSFULLY TREATED BY CLOSED REDUCTION

EDWARD F McLAUGHLIN, M D

PHILADELPHIA, PA

THE ELBOW REGION is a frequent site of bony injury, however, reports of fracture of the capitellum are few, about 100 cases being the total found in the literature to date. One more case is herewith presented and some of its clinical features discussed.

Case Report—Hosp No 28288 M S, white, female, age 20, was admitted to the Germantown Hospital, Surgical Service "B," October 15, 1937, with the history of having fallen down some steps four days previously. Immediate pain was experienced in the left elbow, and difficulty in moving it developed one or two hours later. Any movement caused great pain.

Physical Examination—The left elbow was markedly swollen, and held at a right angle. Movement was greatly limited and very painful. A roentgenogram showed "a fracture of the capitellum of the lower end of the left humerus with a displacement of the fragment forward" (Fig 1).

Ice-bags were placed about the swollen elbow. After 24 hours, a manual reduction, under gas anesthesia, with the aid of the fluoroscope, was attempted, but failed. Bed rest and ice-bags were resorted to once more, and, after two more days, it was decided to attempt closed reduction again before resorting to operative interference. Gas anesthesia was employed. The elbow was held in full extension. With one man pressing firmly upon the anteriorly displaced fragment while holding the lower end of the humerus steady, the other pulled downward on the wrist with great force and hyperextended the elbow. The elbow was then brought quickly up into acute flexion—the fragment slipping into its proper place (Fig 2). A wrist sling was applied to hold the arm in the Jones position. The pain in the elbow was relieved almost immediately and, later the same day, the patient was discharged.

Seen daily thereafter, the sling was removed, the arm lowered to a right angle, rubbed lightly with alcohol, dried, powdered and replaced in a position of acute flexion. After the first week, the patient was seen every other day and the same procedure was carried out. On those days when she did not report the arm was lowered and replaced at home. Three weeks after the fracture was reduced, all dressings were left off and active motion permitted. Two weeks later, the patient was using her arm in all her ordinary tasks. Extension was restricted about ten degrees, but all other movements were completely normal. In ten more days full extension had been regained. A roentgenogram, taken some time later, showed a healed bone (Fig 3). Function has been perfect ever since (Fig 4 A, B, C, D).

COMMENT—Mazel¹ states that "Fracture of the capitellum is so rare that, to date (April, 1935), only 30 cases have been reported in the literature." Lee and Sunney,² in 1934, collected 28 cases, including a series of 17 reported by Lindem,³ and added five of their own. Buxton,⁴ in 1936, discussed 38 cases which had come under his observation at King's College Hospital, from 1933

* Read before the Philadelphia Academy of Surgery, November 18, 1938. Submitted for publication March 17, 1939.

to 1935 Valle,⁷ quoting Becoli's 42 cases, adds one more. There are other, more recent, reports, in which one or two isolated cases are cited^{6, 7, 8, 9, 10}. From the cases noted above, and with allowance for some overlapping, it seems there are now about 100 cases reported in the literature.



FIG 1—Anteroposterior and lateral roentgenograms of fracture of the capitellum before reduction

The first description of this fracture, according to Lee, was made in the autopsy room by Hahn, in 1853. Mazel¹ gives Kocher¹¹ credit for first recognizing and dealing with the condition clinically.

This fracture usually occurs in youth (15 years is the average age given



FIG 2—Anteroposterior and lateral roentgenograms of fracture of the capitellum after closed reduction

in Buxton's series). It probably occurs most often when the arm is extended to break a fall. In this position, the radius is poised behind and below the capitellum, somewhat like a blunt chisel, and is driven against it when the force strikes. If the elbow has been momentarily hyperextended just before

the upward thrust comes, the radius will be in an even more favorable position to chip off the capitellum. The displacement is almost always forward, although in some cases, notably Kocher's, it was posterior. The force in this instance may have been applied with the elbow acutely flexed.



FIG 3—Anteroposterior and lateral roentgenograms of fracture of the capitellum two and one half months after closed reduction

It might be well to recall some anatomic facts. First, that we are dealing *solely* with the capitellum. Second, that this is entirely intracapsular, has no periosteum, and derives its main blood supply through vessels from the joint.

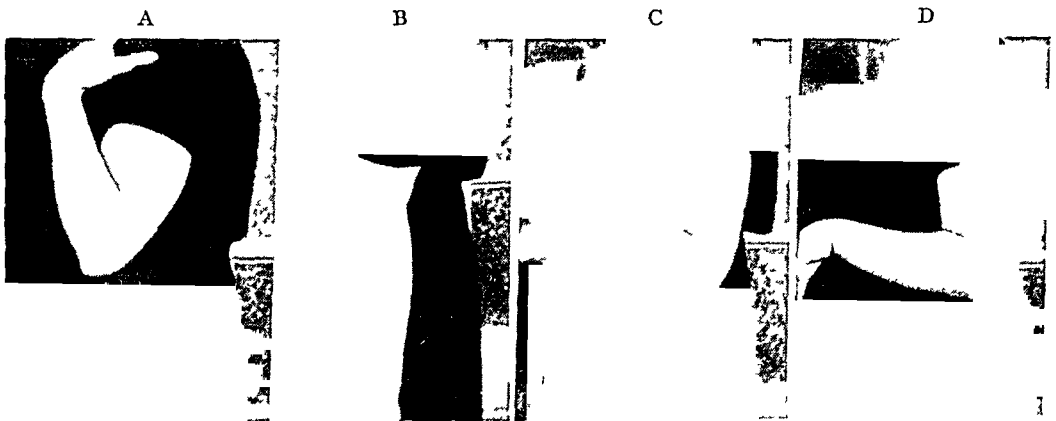


FIG 4—A, B, C and D Showing complete restoration of function of the elbow six weeks after closed reduction of fracture of the capitellum

Third, that the ligament surrounding the elbow joint is weaker anteriorly, where it is sheet-like and pleats up on flexion.

Being an intracapsular fracture, its healing process will depend greatly on whether it is a complete fracture or a greenstick one. If complete, the frag-

ment is severed from any source of nourishment and must be regarded in the light of a bone graft. Its rehabilitation will depend upon new capillaries and trailing osteoblasts bridging the fracture line.¹⁴

Treatment—The desideratum is to restore the normal function to the radiohumeral joint. All depends on whether the capitellar fragment can be restored to its former site and fixed there until it heals. Some feel it can never be properly replaced, or, if it is, it will not become reattached. Fitzgerald¹² says "In all cases, the fragments should be removed as soon as possible after the injury." The chance of the fragment's becoming a loose or fixed foreign body, favored by restricted osteoclastic process, prompts this attitude. Others favor operative reduction and mechanical fixation. Lee favors the employment of a bone peg or steel pin, while Buxton sutures through drill holes or uses a transversely inserted bone peg, running into the trochlea. Immobilization to prevent tearing of the delicate new capillaries with their trailing osteoblasts explains this attitude for mechanical fixation. We feel, and our case illustrates, that once accurately replaced a capitellar fragment can heal without mechanical fixation. In fact, once replaced, all the natural forces in the region tend to hold the fragment in position—the cup-like head of the radius, the humerus, the lateral ligaments, and the ulna all contribute support, all but the anterior ligament. This is compensated for by bringing the radius in front by fixing the arm in acute flexion.

Other authors, also, have clinical proof that healing and function are obtained by this simpler method.^{6, 13} Christopher and Bushnell¹³ report two excellent examples of this. One case, a female, age 40, had complete function 28 days after reduction. Another, age 38, had 90 per cent function in 24 days. Both had union checked by roentgenograms. Their method of reduction was similar to ours. Most of those favoring operative intervention admit some cases may respond to treatment by closed reduction. On the other hand, anyone would be unwise to limit himself to closed methods where indications call for operation, as in old complicated cases, multiple or diversely rotated fragments, *etc*.

Aiding reduction in the case herewith reported was the fact that the swelling had been greatly reduced by the time of the second attempt. Perhaps, if reduction of the fracture cannot be attempted during the first 24 hours, it might better be deferred until after about a week, when the swelling will have become greatly reduced. We should also emphasize that the force used in reducing the fracture in the present instance was more than gentle—almost a sharp, tugging pull.

Treatment after reduction, open or closed, is extremely important. Acute flexion holds the fragments well, and a simple wrist sling permits ready inspection. If swelling occurs, it is unrestricted and any need for changing the degree of flexion will be apparent at a glance. Meyerding and Pollack¹⁰ warn of contracture following too great flexion in the presence of swelling in a case of fractured capitellum.

Early passive motion is most essential—breaking up fibroblastic processes in the traumatized tissue about the joint and not permitting scar tissue to form

Stimulation with light massage, with or without alcohol, nourishes the soft parts, and aids in the circulatory removal of old blood, *etc*

Powdering helps prevent friction and surface necrosis, blistering and infection

Active motion—restricted at first, later unlimited—is the final and best means of restoring function While we did not use it until three weeks had passed, we believe it may be tried even earlier

CONCLUSION

All will agree that restoration of function is the object of any method of treating fractures of the capitellum Most writers admit that an occasional case can be reduced and will get well without operation We feel that a reversal of attitude is needed, that closed reduction with early motion is the method of choice and that other procedures should be reserved for the occasional complicated case

REFERENCES

- ¹ Mazel, M S Jour Bone and Joint Surg , 17, 483, 1935
- ² Lee, W E and Sumney, T J ANNALS OF SURGERY, 99, 497, 1934
- ³ Lindem, M C ANNALS OF SURGERY, 76, 78, 1922
- ⁴ Bunton, St J D Brit Med Jour , 2, 665, 1936
- ⁵ Valle, V Chir d'organ di Movimento, 22, 558, 1937
- ⁶ Ottolenghi, C E, and Lagomarsino, E H Revue orthoped y traumatol , 6, 279, 1937
- ⁷ de Arango, A Rev brasil de chir , 5, 541, 1936
- ⁸ Roberts, N Liverpool Med -Chir Jour , 44, Pt I, 1, 1936
- ⁹ Billi, A Chir de arg de Movimento, 20, 10, 1935
- ¹⁰ Meyerding and Pollock Proc Staff Meet Mayo Clinic, 13, 289, 1938
- ¹¹ Kocher, T Pamphlets, 10-20, 1896
- ¹² Fitzgerald, H W Australia, New Zealand Jour Surg , 4, 414, 1935
- ¹³ Christopher, F, and Bushnell, L F Jour Bone and Joint Surg , 17, 489, 1935
- ¹⁴ May, H ANNALS OF SURGERY, 106, 441, 1937

A SUGGESTED IMPROVEMENT TO THE ALLIS' METHOD OF REDUCTION OF POSTERIOR DISLOCATION OF THE HIP

LEON E. DE YOE, M.D.

PATERSON, N. J.

POSTERIOR DISLOCATION of the hip, with or without fracture of the acetabulum, has become a more frequent injury in recent years. Stimson,⁶ in 1912, states "Percentages of dislocation of the hip, compared with all dislocations was 14 to 2 per cent." Speed,⁴ in 1928, says "approximately 5 per cent of all dislocations admitted to the fracture service of the Cook County Hospital were dislocations of the hip." We have not been able to find more recent statistics dealing with the relative frequency of this injury but believe it to be higher than the 5 per cent reported by Speed in 1928.

The majority of these cases result from automobile accidents and, in our experience, it is the person sitting beside the driver who sustains this type of injury. This has been corroborated by Funsten, Kinser, and Frankel² who, because of the frequency of this etiology in their series of cases, aptly call this injury "dashboard dislocation of the hip."

Campbell¹ observes that fractures of the acetabulum, usually of the posterior lip, were present in 37.5 per cent of his cases of traumatic posterior dislocation of the hip.

It is desirable to radiograph the hip before manipulation to determine the presence or absence of associated fracture of pelvis or femur.

Three methods of reduction are described by Speed:⁵ (1) Allis' direct method (2) Bigelow's circumduction method (3) Stimson's gravity method.

Briefly described, they are as follows: (1) Allis' method (a) Fix pelvis (b) Flex thigh (c) Lift thigh (d) Extend leg.

(2) Bigelow's Method (a) Flex and forcibly lift. If this fails, (b) flex and lift while abducting. If this fails, it will be found that the rent in the capsule will be so large that method (a) will now be successful.

(3) Stimson's method (reverse of lifting and traction). Patient lies face down with pelvis at edge of table. Thighs hang straight down, knee flexed at a right angle, and foot being held by operator. A weight is placed on back of calf of leg just behind the knee.

G. A. Illin,³ in reporting the Dzhadelidze method, describes the technic as follows: "The patient is given a general anesthetic and is placed in a prone position on an examining table in such a manner that both superior anterior spines and the symphysis pubis touch the distal end of the table. The normal lower extremity is placed on a small table of the same height as the examining table. The other extremity is kept with the knee flexed to 90 degrees—it

hangs from the table and is supported by one hand of the surgeon in the region of the calf above the ankle. For the purpose of reduction, pressure is applied to the popliteal region. The surgeon uses his free hand or his knee for this purpose. Simultaneously a rotation of the hip is performed by the hand supporting the lower leg of the patient. This maneuver is followed by a characteristic crepitation of the head of the femur, free mobility of the reduced hip, and restored normal contours of the gluteal region." This method seems to be closely allied to the plan described by Stimson.

Because of the powerful muscles and ligaments with which the hip joint is surrounded, much force is sometimes required, especially if the acetabulum is intact, to pull the head back into the socket. With the patient lying on the floor or a table it is often difficult by means of the above methods for the operator to apply his strength to the best advantage.



FIG. 1.—Photograph demonstrating the author's modification of the Allis' method of reduction of a posterior dislocation of the hip.

At the Paterson General Hospital, during the past 11 years, we have employed a method of applying the principles laid down by Allis, which has resulted in easy reduction in 19 consecutive cases. Because of its simplicity we desire to report it.

Method of Procedure—The patient is anesthetized lying on his back and is so placed that the buttocks are at the end of the table. An assistant holds the normal leg horizontally or it may be placed on a small table of the same height as the operating table. The pelvis is now strapped or firmly held to the table by the assistant. The operator takes the dislocated leg, flexes the thigh, and with his back against the end of the table and against the patient's buttocks, brings the dislocated leg over his shoulder. The operator's shoulder is now under the popliteal space, the knee is flexed, and the back of the patient's

calf lies against the operator's chest (Fig 1) With the leg firmly held in this position the operator lifts upward and bends forward, easily exerting powerful traction on the femur The dislocating force is thus reversed and with an audible click, the head snaps into the acetabulum and the motion of the thigh is no longer restricted

SUMMARY

(1) The methods of reduction of traumatic posterior dislocation of the hip are reviewed

(2) A simple and efficient method is described

REFERENCES

- ¹ Campbell, W C Posterior Dislocation of the Hip with Fracture of the Acetabulum Jour Bone and Joint Surg , 18, 842-850, October, 1936
- ² Funsten, Robert, Kinser, Prentice, and Frankel, Chas J Dashboard Dislocation of the Hip Jour Bone and Joint Surg , 20, 124-132, January, 1938
- ³ Il'in, G A Reduction of Traumatic Dislocation of Hip by Dzhadelidze Method Vestnik Khir , 42, 240, 1936
- ⁴ Speed, Kellogg Text Book of Fractures and Dislocations 709, 1928
- ⁵ *Idem* Text Book of Fractures and Dislocations 755-757, 1935
- ⁶ Stimson, Lewis A Fractures and Dislocations 794, 1912

THE EFFECTS OF TEMPERATURE ON THE SURVIVAL OF ANEMIC TISSUE*

AN EXPERIMENTAL STUDY

BARNEY BROOKS, M D, AND GEORGE W DUNCAN, M D

NASHVILLE, TENN

FROM THE DEPARTMENT OF SURGERY, VANDERBILT UNIVERSITY NASHVILLE TENN

THE REACTIONS of living matter to changes in temperature have been observed and recorded since earliest antiquity. In general, living tissues may be influenced by cooling, warming, freezing and supercooling, and the living tissues may be the whole organism, or an attached part, or a separated part. The effects produced may also be considered from either the viewpoint of an influence on vital processes or as a matter of preservation of viability.

The present communication deals only with the effects of temperature on the preservation of the viability of a part of an animal deprived of its circulation. Previous observations bearing on this particular phase of the problem have been reported by Starr,⁷ Allen,^{1 2 3 4, 5} and Freeman.⁶

Starr placed the extremities of a series of patients suffering from peripheral vascular disease in different environmental temperatures and noted the effects on the usual criteria of the efficiency of the circulation. With the color as an index of the volume flow of blood, and pain as an indicator of tissue damage, he concluded that the maintenance of a temperature of 30° to 34° C was most favorable for increasing the circulation and inhibiting unnecessary oxidation.

The first experimental study of the possible beneficial effects of cooling a part of the body with deficient circulation in the prevention of gangrene was recorded by Allen,^{1 2 3 4, 5} in 1937. He experimented with rats, cats and dogs. The extremities and loops of intestine were rendered ischemic by ligation of arteries and the application of tourniquets. The environmental temperatures were obtained by the immersion of the ischemic part in melting ice or warm water. It was found that gangrene occurred after only three to three and one-half hours if the temperature of the ischemic part was maintained at 40° to 41° C, and did not occur after 54 hours of ischemia if the part was kept at 0° to 2° C. Allen thoroughly appreciated the inaccuracies of the methods employed, which he states were the only ones available to him. The amount of ischemia produced by ligation of an artery is well known to vary widely in different experiments, and it is always impossible to determine the extent of local damage of a tourniquet. His experiments dealt only with temperatures between 38° and 47° C, around 0° C, and room temperature.

More recently, Freeman⁶ has reported a study of the influence of tempera-

* Read before the American Surgical Association, St. Louis, Mo., May 3, 1940.
Submitted for publication May 3, 1940.

Aided by a grant from the Council on Physical Therapy of the American Medical Association.

ture on the development of gangrene in instances of peripheral vascular disease. He believes that raising the temperature of an ischemic extremity increases both the blood flow and the metabolism, but that in the presence of diminished blood flow the relatively larger increase in the latter may produce a greater nutritional deficiency and, as stated by Freeman, "Gangrene results

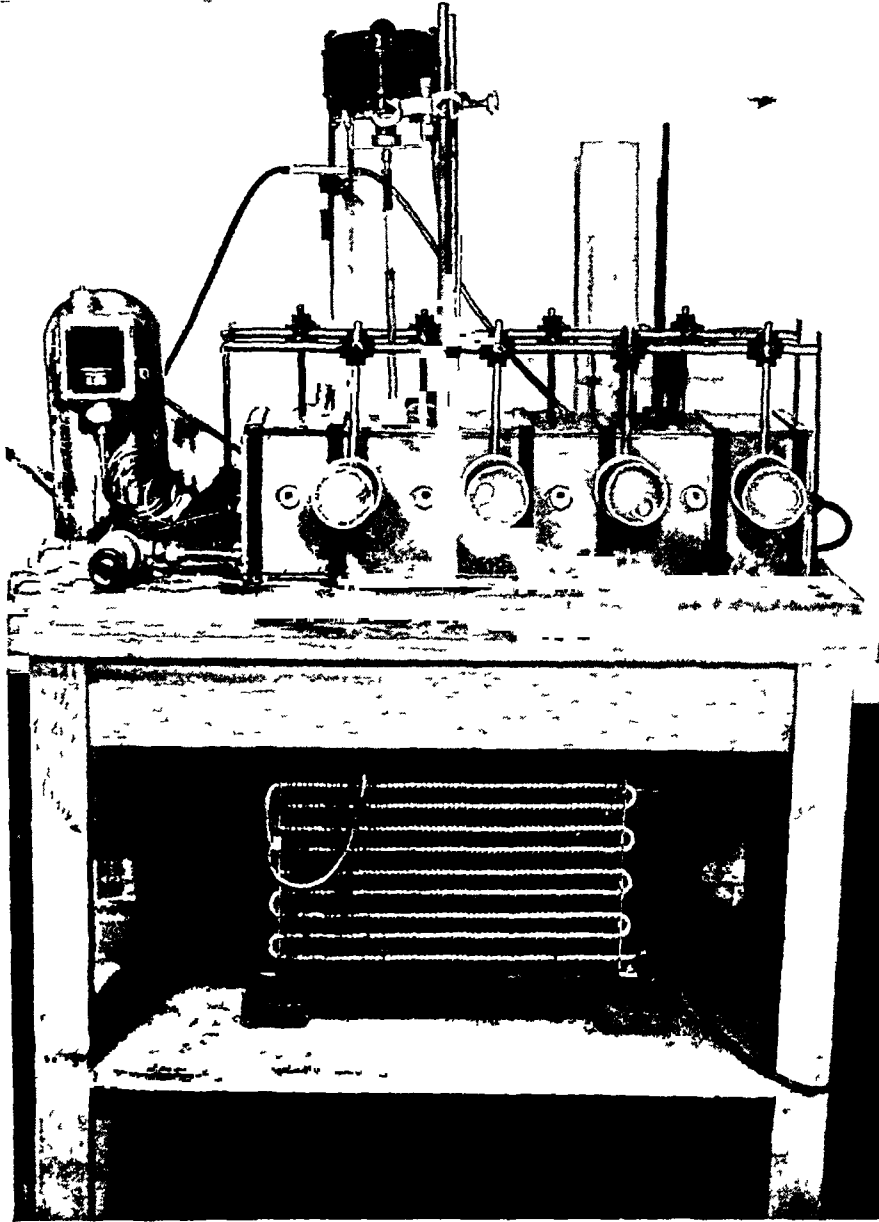


FIG 1—Apparatus employed for maintaining low temperatures. The compressor for the refrigerant is on the lower shelf. Four of the eight rats are shown in the containers, as are also the rubber tubes containing the tails of the rats on the opposite side. The thermostat is on the left, the motor above drives the stirring apparatus. The pressure was applied within the chamber through the rubber tube at the extreme right.

from a discrepancy between the demands of the tissues and the supply of blood to meet these nutritional needs." Freeman recommends maintenance of the temperature of the air about an ischemic extremity at 30° to 34° C. From this, it is clear that Freeman believes the anemic extremity should be warmed by a surrounding air which is approximately at the same temperature as the average normal warm foot.

In a previous communication the authors⁸ have reported a study of a series of experiments in which different pressures were applied to rats' tails for different periods of time. In this previous experimental study a remarkably constant set of conditions were found which seemed particularly appropriate for the study of the effects of temperature on the viability of tissues which were deprived of circulation. It was found that if a rat's tail were subjected to a pressure of 130 Mm Hg for a period of 18 hours at room temperature, massive gangrene subsequently occurred in all instances. The time factor was so sharply defined that gangrene was never produced by pressure applied for less than 17 hours at room temperature.

The present experiments consisted in determining the minimum time for applying a pressure of 130 Mm Hg to a rat's tail maintained at a given tem-

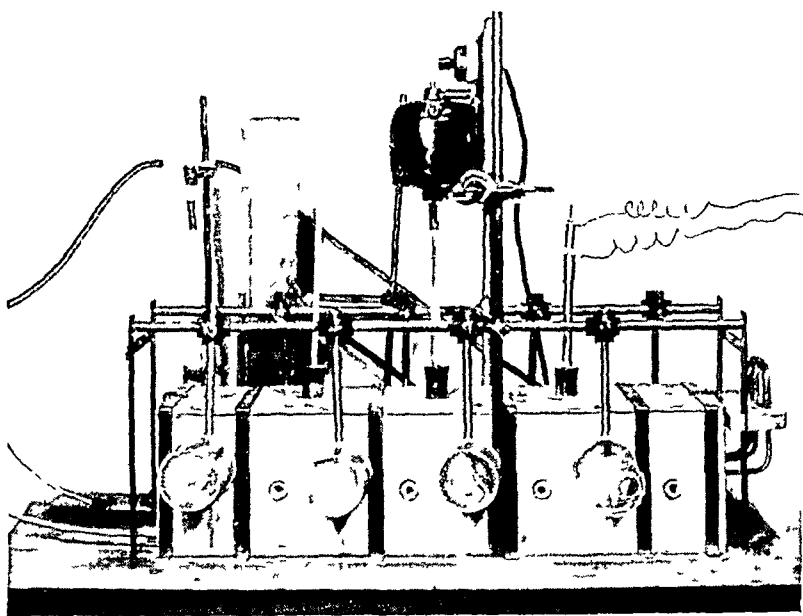


FIG. 2—Apparatus employed for maintenance of temperatures 15° C and above. The mechanism for pumping the warm or cold fluid is not shown in this photograph. The coiled wires connect with the thermostatic control.

perature which would insure the subsequent development of gangrene after the animal had been returned to room temperature. The apparatus employed was similar to that previously described except for the use of a larger chamber, which permitted experiments to be conducted on eight animals simultaneously, and the addition of apparatus for the maintenance of constant temperatures within the range of -5° to 40° C.

The apparatus (Figs. 1 and 2) consisted of a closed, rectangular copper box across which were stretched eight thin-walled rubber tubes (Penrose tubing) into which the rats' tails were placed. A constant pressure of 130 Mm Hg was maintained within the box by compressed air and a suitable mercury valve. One box contained a coil of copper tubing which served as the expansion chamber for SO₂ fed to the coil by a compressor obtained from a small commercial refrigerator. In another box the coil served to conduct hot water fed by a small electrically driven pump. The supply of the re-

frigerant or heating medium was controlled by thermostats sensitive to one or two degrees' temperature change. The sensitivity of the thermostats and the even distribution of the chosen temperature to all parts of the box were controlled by partially filling the chamber with dilute alcohol which was subjected to continuous, vigorous agitation by an electrically driven stirrer.

The temperatures chosen for the experiments were -5° , 1° , 5° , 15° , 30° , 35° and 40° C. Maintaining a constant pressure of 130 Mm Hg, successive groups of rats' tails were subjected to each temperature until the length of time for the uniform production of gangrene was determined.

It is important to emphasize that the rats' tails were not left in the pressure chamber until gangrene was present, and the time assigned as that necessary to produce gangrene, is the length of the period during which pressure and temperature were maintained in such instances as gangrene subsequently developed at room temperature. Although it was possible in some instances to predict the occurrence of gangrene at the time of the termination of the pressure and temperature, the actual state of gangrene did not occur until 8 to 24 hours later. If gangrene did not develop the animals were sacrificed after varying periods of observation and microscopic sections of the tails prepared.

The results of the experiments are summarized in Tables I and II. Table I shows the results obtained in 117 of the 140 experiments performed. Table II shows the minimum periods at each temperature in which gangrene subsequently occurred at room temperature.

TABLE I

Temperature Centigrade	Number of Hours	Number of Animals	Incidence of Gangrene	Temperature Centigrade	Number of Hours	Number of Animals	Incidence of Gangrene
40° C	1	1	0	15° C	18	1	0
	2	3	0		24	1	0
	3	5	2		30	2	0
	4	9	9		36	5	0
	5	5	5		48	8	8
35° C				5° C	72	3	3
	5	2	0		24	2	0
	6	2	0		30	2	0
	7	2	0		36	3	0
	8	4	3		48	7	0
	10	5	5		72	8	0
30° C	12	2	2	1° C	96	1	1
	8	2	0		18	2	0
	10	3	0		30	2	0
	12	3	1		40	2	0
	14	6	4		72	3	0
	16	5	5	-5° C	96	4	0
					8	2	2

From an examination of Table II, it is obvious that the effectiveness of temperature became proportionately greater toward either the highest or the lowest temperatures studied. Diminishing the temperature from 15°

to 1°C added at least 48 hours to the duration of viability, and increasing the temperature from 35° to 40° diminished the period of viability more than one-half

TABLE II

DURATION OF ANEMIA NECESSARY FOR PRODUCING GANGRENE AT VARIOUS TEMPERATURES

Temperature Centigrade	Number of Hours
1°	96 plus
5°	96
15°	48
30°	14-16
35°	8-10
40°	3-4

It was impracticable to submit animals to confinement for more than 96 hours, and this period of confinement was attended by a relatively large proportion of the animals dying during the period in which pressure was being applied. In two experiments the rats' tails were subjected to a temperature of -5°C for eight hours without pressure being applied. In each instance the tail was frozen and gangrene developed. In four other experiments gangrene occurred after the tails were frozen by immersion in alcohol at -75°C . No attempt has been made to obtain supercooling as employed in the experiments of Lewis.⁹

The pathologic changes following different periods of ischemia at various temperatures in which gangrene did not occur were similar to those observed in the experiments previously reported. It is, however, worth calling attention to the fact that marked fibrous replacement of muscles was observed in instances in which the maintenance of a low temperature has prevented the occurrence of gangrene.

These experiments demonstrate conclusively that temperature is a powerful factor in determining the length of time tissues rendered completely anemic remain viable.

In these experiments there has been no attempt to determine the mechanism by which temperature exerts an influence on viability of tissues completely deprived of circulation. It is worth while pointing out, however, that the influence of the temperature on viability of the rats' tails in these experiments was not because of any change in the receipt of nutritive material or the removal of waste products. In other words, the condition as far as the circulation was concerned was presumably the same at each temperature. Although these experiments might be used as further evidence that temperature may influence the development of gangrene because of an alteration of metabolism, we believe that this argument should not be presented until more definite information is obtained. Furthermore, it is important to recognize that the term gangrene as applied in clinical medicine to conditions developing from peripheral vascular disease designates postmortem changes rather than connoting evidences of necrosis, and it is well-known that temperature is a

powerful influence on the particular postmortem changes constituting the clinical picture to which the term gangrene is applied

The uncertainty of determining by gross examination the exact time at which necrosis occurs is illustrated in these experiments, in which it was frequently impossible to determine at the end of a period of continuous application of pressure if the tail were subsequently to undergo desiccation and spontaneous amputation. In fact, if gangrene did occur there still remained a doubt as to the exact time of cessation of viability. It may be added, however, that microscopic sections of tails subjected to conditions uniformly found to cause gangrene often show definite microscopic evidence of cell disintegration at the time of cessation of the period of anemia. This is important in interpreting Stann's statement that he had observed that baking



FIG. 3—Photograph showing characteristic appearance of gangrene. Obtained five days after removal of the tail from the pressure chamber

of an extremity resulted in the rapid development of gangrene. Two experiments have been performed to illustrate this point. Two rats' tails were subjected to a pressure of 130 Mm Hg at 30° C for 16 hours, which in five previous experiments produced gangrene in all instances. At the end of this period both tails were equally blanched and neither was gangrenous. The tail of one animal was immediately transferred to a chamber in which the temperature was 1° C. The temperature of the chamber of the other rat's tail was elevated to 40° C. No further pressure was applied to either tail. The tail maintained at 40° C showed marked discoloration in two hours and definite disintegration at 12 hours. The tail maintained at 1° C showed no evidence of gangrene at the end of 24 hours. In fact, the tail appeared as if gangrene would not occur. The tail was removed from the cold chamber and the animal returned to room temperature. Evidences of gangrene appeared in 24 hours. Additional experiments are being performed to study the condition of the circulation in rats' tails in periods intervening between the cessation of pressure and the subsequent appearance of gangrene.

In conclusion, the authors wish to emphasize that the results of these

experiments are not adequate evidence for the immediate acceptance of value in clinical medicine of methods of refrigeration of extremities rendered presumably temporarily anemic by peripheral vascular disease. First, there was definite evidence in the microscopic study of the rats' tails which did not become gangrenous that extensive fibrous replacement of such highly specialized tissues as muscles and nerves may take place, although refrigeration had prevented massive necrosis. Second, conditions were present in these experiments which are very unlikely to be duplicated in clinical medicine. In



FIG. 4.—Photomicrograph of rat's tail made 15 days after subjection to 130 Mm Hg pressure for 48 hours, at 1° C. Although gangrene was averted by low temperature, degeneration and fibrous replacement of the muscle can be seen.

the experiments there was a relatively thin part of the body completely deprived of circulation by pressure. This presumably produced a relatively narrow transitional zone between the normal and modified tissues. In clinical medicine the thickness of the part, the broad transitional zone not well-defined by transverse planes, and the absence of signs permitting the determination of impending necrosis make it probable that the possible beneficial effects of refrigeration in preventing gangrene will be solved not by laboratory experiments but by statistical data derived from clinical experience.

Before the adoption of refrigeration as a method for the maintenance of viability of free transplants of tissue, such as skin grafts, it will be necessary

to know the influence of refrigeration not only on the preservation of viability, but also its influence on various factors involved in the healing of wounds

REFERENCES

- ¹ Allen, F M Am Jour Surg , 45, 459, 1939
- ² Allen, F M Surg , Gynec , and Obst , 67, 746, 1938
- ³ Allen, F M Surg , Gynec , and Obst , 68, 1047, 1939
- ⁴ Allen, F M Surgery, 3, 893, 1938
- ⁵ Allen, F M Tr Assn Am Phys , 52, 189, 1937
- ⁶ Freeman, Norman E Arch Surg , 40, 326, 1940
- ⁷ Starr, I, Jr Am Jour Med Sc , 187, 498, 1934
- ⁸ Brooks, Barney, and Duncan, Geo W Arch Surg , 40, 696, 1940
- ⁹ Lewis, Thomas, and Love, W S Heart, 13, 27, 1926

THE FUNCTION OF THE VERTEBRAL VEINS AND THEIR RÔLE IN THE SPREAD OF METASTASES*

OSCAR V. BATSON, M A , M D

PHILADELPHIA, PA

FROM THE GRADUATE SCHOOL OF MEDICINE, UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA, PA

METASTATIC ABSCESSSES and metastatic tumors can appear in locations that do not seem to be in line of direct spread from their primary focus. There is even a regularity of distribution of these paradoxical metastases. Empirically, the roentgenologist makes a diagnosis of primary carcinoma of the prostate when he finds a certain peculiar distribution of bone lesions in the pelvis. Adequate explanation has not been forthcoming for the typical and peculiar distribution of these metastatic lesions. The pattern, to me, is not at all that of the nerve sheaths of the area as suggested by Warren, *et al*¹. It is not the pattern of lymph vessel distribution. The only anatomic system into which this pattern fits is the system of veins which, in its plexiform ramifications, infiltrates and invests the sacrum, the lumbar spine, and the adjacent wings of the ilia. Several years ago, I suggested that the architecture of this plexus of veins could be exploited by taking advantage of the pelvic anastomoses of the deep dorsal vein of the penis. The connections and the collateral circulations of this vein are identical with those of the prostatic plexus of veins with which it connects. Valves in the veins of this region are exceedingly variable. All valves present permit flow toward the sacral venous plexus. Injections were first made in 1937. A preliminary report was read before the Conference of Eastern Radiologists, in Philadelphia, January 29, 1938, under the title of "The Veins of the Sacrum in Relation to Metastatic Carcinoma from the Prostate." This work has been continued and extended. Injections and corrosion preparations of the vessels of the head and neck, already completed, formed an invaluable background for this study. The dissemination of infections and tumors from organs in other regions by the veins about the spine has also been considered. This has led to a better appreciation of the rôle of the vertebral veins in normal physiology.

CADAVER INJECTION EXPERIMENTS

Experiment 1—In our first injection experiment we lifted the dorsal vein of the penis, in an adult cadaver, near the symphysis pubis and injected a thick radiopaque material toward the pelvis. Specifically, we used Weber's,

* Part of the material of this paper was given in an address before the Philadelphia Laryngologic Society, March 5, 1940, under the title, "The Circulation of the Head, Especially Venous, with Reference to Osteomyelitis, Brain Abscess and Malignant Metastasis." Part was also presented before the Philadelphia Neurologic Society, March 22, 1940, under the title, "The Cerebrospinal Veins."

Submitted for publication June 5, 1940

King's yellow, artist's tube water color. This was selected because its brilliant color allows it to be readily followed in tissues, further, it is radiopaque. The course and progress of the injection was followed under the fluoroscope. The mass entered the prostatic plexus of veins, passed along vessels of the lateral pelvic wall into the common iliac vein of either side and then to the vena cava inferior. As can be seen from the accompanying roentgenogram (Fig. 1) the right iliac artery compressed the vein at the point at which it crossed it. The lateral sacral veins are well injected. In the stereoscopic films of this pelvis, the material can be followed into the bone and into the sacral canal. Some material spread into the wings of the ilium. These



FIG. 1



FIG. 2

FIG. 1—Anteroposterior roentgenogram of pelvis of male cadaver following the injection of thick radiopaque material into the deep dorsal vein of the penis. Note the extension of the injected mass into the sacrum.

FIG. 2—Anteroposterior roentgenogram of pelvis of a male cadaver injected with a thin radiopaque material through the deep dorsal vein of the penis. The injected material has rather completely infiltrated the venous circulation of the pelvis itself.

roentgenograms give us a pattern which seems an exact replica of the pattern made by the early spread of carcinoma of the prostate. It was surmised that the parallelism would be even more striking with a more complete injection.

Experiment 2—In the next cadaver, in order to secure a good injection of vessels of small caliber, a "fine" or thin injection mass was used. We employed Weber's artist's water color vermilion because in our experience it casts an excellent roentgenographic shadow in extreme dilutions. This preparation of the native sulphide of mercury was diluted with water until it was of the consistency of a light machine oil. The injection was again made into the dorsal vein of the penis under fluoroscopic control. As before, the cadaver was in the dorsal recumbent position. We used an ordinary 20 cc glass syringe and light pressure with the thumb or index finger. No resistance to injection was encountered, at times the plunger would close part way of

itself This time, to our surprise, none of the material reached the inferior vena cava but instead spread out in the veins in and about the sacrum itself The veins of the ilium and those of the lower lumbar spine were also injected

This injection still better duplicated the pattern of metastatic spread from the prostate but it raised the question as to why the mass did not enter the vena cava inferior The mass was thin and met with no resistance in the

veins about the dura and those in and about the vertebrae The cadaver was in the dorsal recumbent position and hence the vena cava inferior was at a level several centimeters higher than those veins that were so readily filled The heavier, more viscid mass in the first injection spread more rapidly in the channels of large caliber To study further this vertebral spread, it was decided to use a larger quantity of the thin mass for the next injection

Experiment 3—A cadaver was prepared as before Fluoroscopic control was used, and after the injection of measured amounts of mass, 10entgenograms were made At no time did the fluid enter the caval system of veins (Fig 2) The material progressed up the spine through successive anatomic regions Many intercostal veins were filled as well as the veins of the bony pelvis

When the amount of injection mass was increased to a total of 200 cc, the material attained the base of the skull and entered the cranial cavity The mass also extended along fine straight vessels into the right thigh (Fig 3) These were found to be vasa vasorum, or, more specifically, venae vasorum of

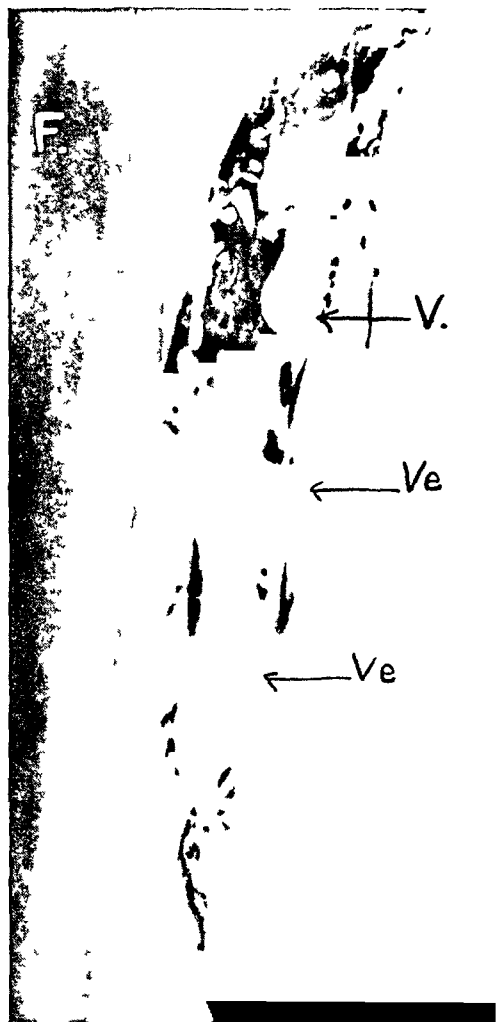


FIG 3—The same cadaver as Fig 2 showing the injection of the venae vasorum of the femoral vessels F femur V valve, Ve, venae vasorum

the femoral vessels Valves prevented the filling of other, larger veins of the thigh

Although the vertebral plexus of veins of the upper thoracic and cervical regions was familiar ground from our earlier preparations, we were not prepared for this extensive filling of the vertebral veins and the by-passing of the caval veins This specimen furnished a composite picture of the metastatic pattern of advanced cases of carcinomatosis with primary origin in the prostate

Repeated experience has shown that the extent and course of this injection was not an accident. It has been made repeatedly and the course examined roentgenographically and by dissection. This method of venous injection has for two years been routine in the preparation of male cadavera for dissection in this laboratory. We use a latex rubber mass² and expect to find fairly well filled such veins and sinuses of the cranial cavity as the superior longitudinal sinus, the cavernous sinus, Trolard's anastomotic vein and others.

ANIMAL INJECTION EXPERIMENTS

Our next interest was to see if this pattern of venous flow could be duplicated in a living animal or if it was but an artifact of cadaveric experiment. This entire system of epidural and vertebral veins has a free and rich anastomosis at each spinal segment with the veins of the thoraco-abdominal cavity. It is a system of veins without valves except in minor connecting channels. The pressure in the system is very low. With every compression of the trunk, such as is done many times daily in straining, in lifting, in coughing, in holding one's breath, it seemed to me that the intra-truncal pressure would be raised to a sufficient height so that blood would flow, not into the inferior vena cava, but into this vertebral system of veins. In order to test this hypothesis the following experiment was carried out on the monkey.

Animal Experiment 1—With an aseptic technic and sodium amytal as an anesthetic, the deep dorsal vein of the penis of a *Macacus Rhesus* monkey was isolated and a small cannula inserted. The cannula tip was directed toward the pelvis. Colloidal thorium dioxide, prepared for roentgenologic diagnosis, was injected with a hypodermic syringe into this cannula. The roentgenogram (Fig 4A) shows that the material passed into the pelvis, followed around the pelvic wall and ascended the trunk by means of the inferior vena cava. We feel that these roentgenograms represent the ordinary course of flow during trunk muscle inactivity. In order to, in part, simulate conditions of increased intra-abdominal pressure such as produced in coughing or straining, a towel was tied about the monkey's abdomen and an injection was again made (Fig 4B). Under this condition, while some of the material entered the inferior vena cava it ascended only part way, some of the thorium medium passed into the vertebral system of veins and can be followed in the roentgenogram past the zone of compression into the vessels of the thoracic spine and out into the lower intercostal veins. Here then, in the living animal, under simulated physiologic conditions, we have a flow which parallels the injection made in the human cadaver, and one which duplicates the pattern of prostatic carcinoma spread.

Animal Experiment 2—This experiment was repeated on a second monkey with identical results. These results were so clear cut that it did not seem necessary to enlarge the series.

These experiments indicate that during the Valsalva maneuver, namely, compression of the chest and abdomen with the larynx and other sphincters closed, not only is the blood prevented from entering the chest by way of veins, but blood is actually squeezed out of the intra-abdominal veins into the vertebral vein system. The increase in intraspinal or intracranial pressure during the Valsalva maneuver or during its physiologic counterpart—coughing, sneezing, *etc*—is, therefore, active and not passive. It is possible that the intrathoracic and the intra-abdominal pressures may not always parallel each other. Hamilton *et al*³ studied coughing, *etc*, but were concerned with the arterial blood pressure and the spinal fluid pressure and not with venous pressure. It should be pointed out that any condition accompanied by coughing or straining would tend to increase the flow into this venous system, and

this may account for the high incidence of cranial metastases in lung abscess and bronchiogenic carcinoma

SUMMARY—The injections in the live animal were not essentially different from those obtained in cadavera, and show that the cadaver injections were not artifacts

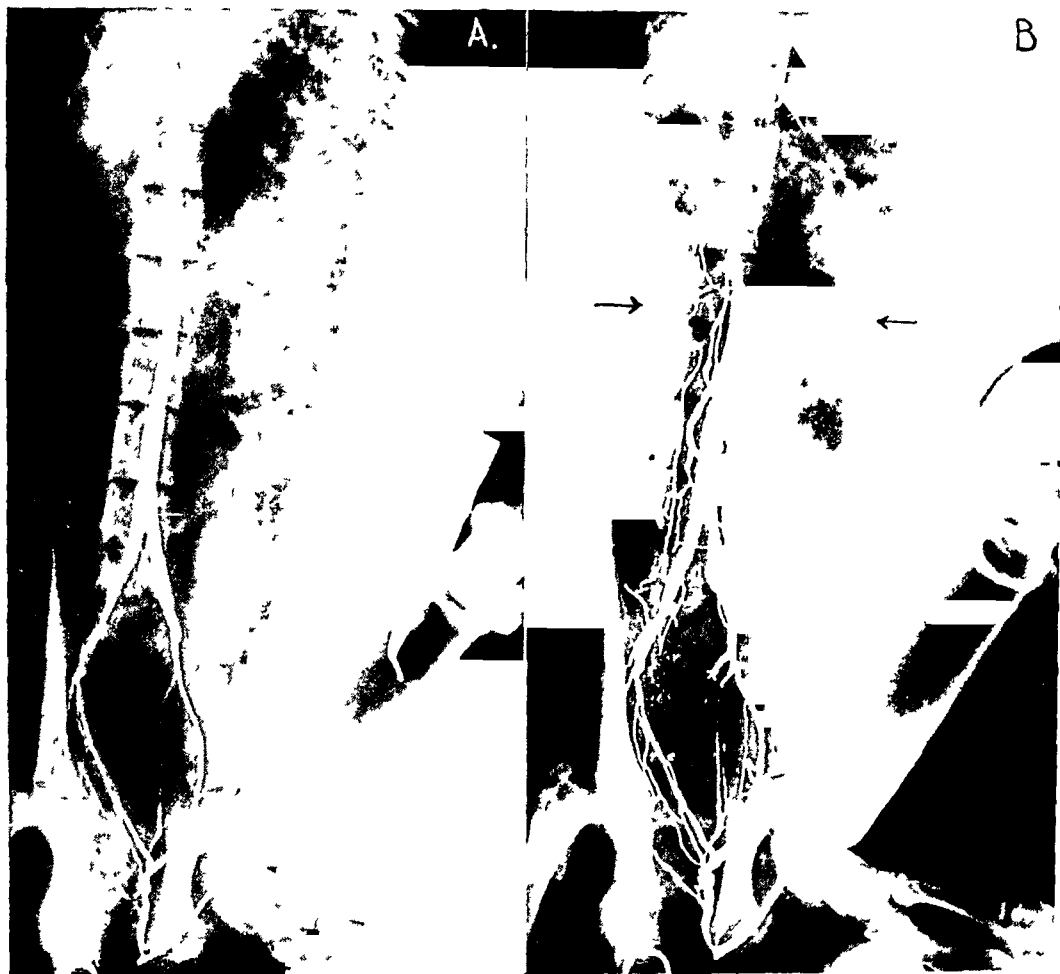


FIG. 4. A—The roentgenogram of living monkey during injection of colloidal thorium dioxide into the deep dorsal vein of the penis. The injected material passed upward through the inferior vena cava. B—The same animal as A during injection following abdominal compression with a towel. The material no longer follows the inferior vena cava but passes upward through the vertebral veins and is visualized in lower intercostal veins.

CADAVER INJECTION EXPERIMENTS IN OTHER REGIONS

Breast tumors also give rise to many "paradoxical" metastases. To see whether a venous pattern would reflect the grouping of aberrant metastases from breast carcinoma, an injection was made into a small vein in the left breast of an adult female cadaver. The cadaver was in the dorsal recumbent position and although two venules were cannulized, the injection was made in only one. A watery, thin mass composed of artist's water color vermilion (mercury sulphide) was injected. With the injection of 30 cc, the material was found in the clavicles, in the intercostal veins, in the head of the humerus, in the cervical vertebrae, in the transverse cranial venous sinus, and even in

the superior longitudinal sinus (Figs 5A and 5) Some of the material was also to be found in the azygous vein and in the superior caval system These injections parallel the spread of many of the so-called aberrant metastases from the breast, for example those to the paranasal sinuses, to the skull bones, to the cervical vertebrae and to the shoulder girdle, *etc* This injection has been repeatedly duplicated

In a recent breast injection in a senile female, a small cannula was introduced into a vein just lateral to the areola mammariae The first 15 cc of the injected material spread entirely into the adjacent subcutaneous tissue The skin surrounding the site of injection flushed and this flush gradually extended past the midline Only after the injection of more than 15 cc did the mass progress into the intercostal veins and to the vertebral system of veins, and into the shoulder girdle In the roentgenographic stereoscope, the radiopaque mass is seen in the coracoid process of the left scapula and in the head of the right humerus The spread of injected material in the subpapillary plexus of the skin indicates that Handley's lymphatic permeation theory, even as it concerns the skin, might be restudied with profit Further injection studies of the venules of the breast always resulted in an erythematoid cutaneous blush, often this spreads past the midline into the other breast The veins



FIG 5—Composite anteroposterior roentgenogram of female cadaver after injection of radiopaque material into a venule of the left breast Note the extensive filling of the vertebral veins the superior longitudinal sinus transverse sinus as well as in other dural and cerebral veins

present a network rich enough to explain permeation should the microscopy of tumor cases indicate their invasion. Possibly both lymphatics and venules are concerned in tumor spread in the skin.

The parallelism between the architecture of the injected venous network and the pattern of distribution of metastases brings up the entire problem of the mechanism of tumor spread.

THEORIES OF TUMOR SPREAD

Objections are constantly occurring to current theories of tumor spread. Objections of Handley's⁴ permeation theory are very completely stated by

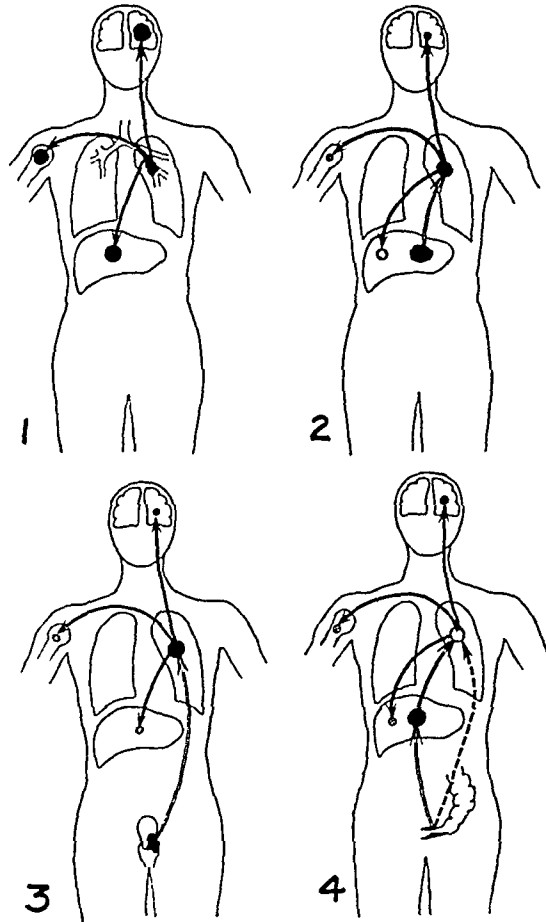


FIG 6—Walther's concept of tumor spread from various regions: 1) primary lung tumors; 2) primary liver tumors; 3) tumors from the area drained by the caval system; 4) tumors from the area drained by the portal system.

Willis.⁵ A clear summary of the whole problem, together with his own concept of tumor spread, is made by Walther,⁶ who holds that metastases are carried by lymphatic channels only so far as regional lymph nodes, from that point on he feels that tumors are spread by the blood-vascular system. His views are shown in four clear-cut figures (Fig 6) to illustrate his four types. He cannot concede the possibility of a retrograde lymphatic spread (Handley), and while he admits in theory the possibility of a temporary reversal of the flow in a vein, he does not think that this has any practical significance. Walther did not envision the rôle of straining and coughing

in tumor spread stated above. It is to be noted in each of Walther's four types, namely, the lung, the liver, the portal and the caval, that he takes the metastatic material by way of the caval system through the heart, through the lungs, back through the heart and then to the peripheral parts of the body. This makes necessary his assumption of differential filters to explain the absence of lung lesions. It seems doubtful that an assumed predilection of carcinoma cells for tissues invaded routinely, explains the distribution pattern in such conditions as metastatic carcinoma of the prostate.

The transporting of tumor cell masses in veins is established by numerous reports (see Willis,⁵ p 18). The rôle of veins in the spreading of pyogenic processes needs no comment.

According to the concept here developed we have a vast intercommunicating system of veins which on the ground of anatomic injections, animal experiments, and simple logic, is constantly and physiologically the site of frequent reversals of flow. During these reversals a pathway up and down the spine exists which does not involve the heart or the lungs. The pathway has many connections. It provides a ready vehicle for the explanation of "aberrant" metastatic patterns and removes the stumbling block of the absence of lung involvement. The course through an open foramen ovale, while still a possible path, is no longer necessary to explain this lung "paradox."

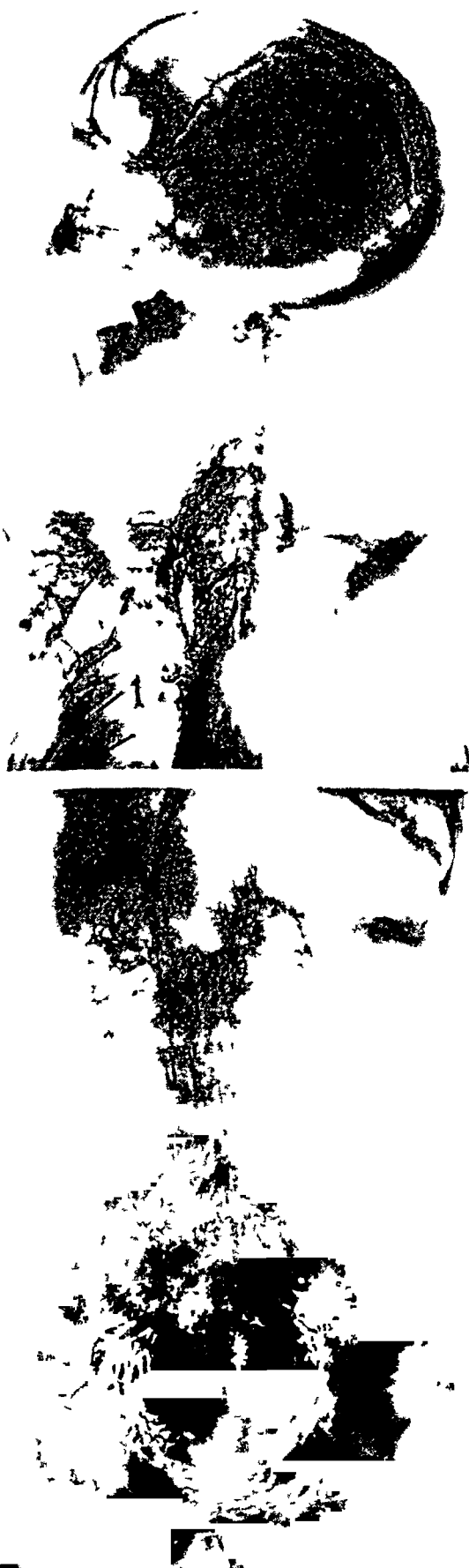


FIG 7.—Composite roentgenogram of small male cadaver. Injection of radiopaque material into deep dorsal vein of penis. Note extensive cranial vein injection.

THE VERTEBRAL VEINS AND CONNECTIONS

I have referred to these veins about the vertebral column with their connections as the vertebral veins. Sometimes they are designated as the meningeo-rachidian veins. The strictly vertebral portion of the network is composed of thin-walled vessels, when empty of blood they are difficult to identify yet they have considerable volume. Gilbert Breschet⁷ was the first to fully appreciate the complexity and interrelationship of these veins of the skull and vertebral column. In the head and neck in man the veins ordinarily have no valves except at the point of emptying of the internal jugular veins. Throughout the cranium the veins of the brain, the veins of the meninges (the venous sinuses), and the veins of the skull bones themselves (the diploic veins), and the veins of the various extracranial plexuses anastomose richly. The usual methods of study fail to indicate their extent and size. Study of these vessels in the cadaver, in the experimental animal, and at the operating table show that they are storage lakes⁸ as well as pathways of drainage. Stagnation is frequent. Their thin walls indicate that their contents are under low pressure.

The longitudinal vertebral veins duplicate their size and pattern from segment to segment, they have connections with the veins of the body cavities at each intervertebral space. The head, except for the two internal jugular veins, has a very similar arrangement. Even with the jugular veins, the posterior condyloid veins and the mastoid emissary veins and others act as by-passes, and are part of a plexiform network.

These vertebral veins have many and rich communications with the veins in the spinal canal, the veins around the spinal column, and those within the bones of the column. This system communicates with the segmental (intercostal) veins of the thoracico-abdominal wall (including those of the breast) and with the azygous system of veins. Through the latter there are free communications with the posterior bronchial vein and the parietal pleural veins. There are an occasional communication with a renal vein and rich communications with the pelvic viscera. Many of these communications are seen in a recent injection.

In a five-foot four-inch senile, male cadaver, weighing but 65 pounds, we were able to readily introduce 200 cc. of medium into the meningeo-rachidian system by means of the dorsal vein of the penis. A study of the roentgenograms of this cadaver shows that there has been some spill-over into the caval system. Apparently, this occurred through one of the lumbar veins, and the material ran from there in a retrograde fashion into the renal and to a lesser degree into an hepatic vein. Even discounting for this spill into caval connections the amount of material injected, in the absence of back

* Barcroft, according to Franklin⁶ feels that an organ can be regarded as a blood depot only if it is clear "that the blood is not in the organ because it is being used there." Willis, however, fails to include this vertebral plexus in his list of blood depots. This seems to be an oversight, for the vertebral veins contain blood obviously not in use in the region.

pressure to cause distention, represents a considerable amount of fluid when rated against the total amount of blood in a small individual

The testes and ovaries do not ordinarily have direct connections. These veins of the spine connect with the venae cavae of the large vessels of the extremities and with the veins of the two bony girdles and the veins of upper ends of the femora and humeri. For the most part, all of the vessels mentioned are without effective valves. The valves of the pelvic veins are variable. The veins accompanying the spinal nerves are commonly described as having valves but, as seen by the injection (Fig 7), these valves are no barrier to the suffusion of the entire system. Developmentally, while this system came from many components it has retained its essential primitive character—rich anastomoses, absence of valves, plexiform channels and many reduplications.

THE VERTEBRAL VEINS AS A VEIN SYSTEM

It is proposed that in addition to the recognized systems of veins, the pulmonary, the caval and the portal, because of its anatomic structure, its physiologic and its pathologic importance we add, as a fourth, the vertebral system of veins (Fig 8). According to this concept, in every act of straining, coughing, or lifting with the upper extremity, the blood is not only prevented from entering the thoraco-abdominal cavity it is actually squeezed out of the cavity. Tumors and abscesses of the thoraco-abdominal wall, including the breast tumors of the lung, pelvic tumors and abscesses, lesions of the shoulder and pelvic girdles, and occasionally tumors and abscesses of other organs have connections with this vein system and may therefore, have metastases distributed anywhere along the system without involving the portal, the pulmonary or the caval system.

IMPLICATION AND EXTENSION OF CONCEPT

Almost every medical journal, medical meeting and hospital corridor provides case reports which are understandable by the mechanism here reported but which otherwise are obscure. Recent reports (Weyrauch,⁹ and Walsh and Goldberg¹⁰) of disaster following diagnostic injections of peritoneal air, and of blindness after pneumothorax are, unquestionably, to be explained by the intro-

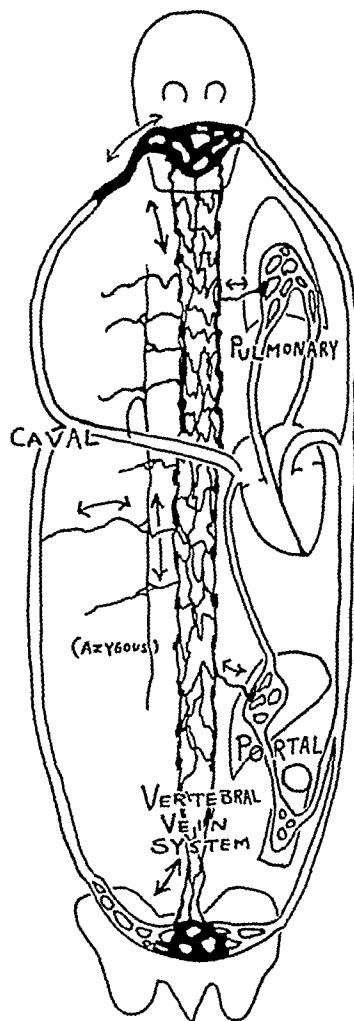


FIG 8—Diagram indicating the possibility of spread of tumors and abscesses from and to various regions of the body through the vertebral vein system which by passes the caval, the portal and the pulmonary vein systems

duction of an emboli into the vertebral venous system. This venous an embolism problem is now being studied in experimental animals and will be reported shortly (Batson, Webster, MacDonald and Lewy)

Other applications to some of the problems raised by spinal cord tumors and by ascending spinal infections will immediately occur to many

Turner and Jaffe¹¹ have recently summarized a large series of cases in regard to metastases. They note the tendencies of the various histologic types, but even after this classification, much is unexplained if the vertebral veins are not utilized. Omond¹² reports a case of cancer of the penis in which the spread probably occurred through the vertebral veins. These veins seem to explain why the neurosurgeon so frequently makes the diagnosis of bronchiogenic carcinoma with cranial metastases. The primary lesion provides the tumor cells and the stimulus for the cough which causes a flow from the bronchial veins, especially the posterior one, into the spinal veins rather than into the veins of the right heart. One would expect metastases to travel both upward and downward. Folsome¹³ reports two cases of vaginal tumors, secondary to bronchiogenic carcinoma. The uterovaginal veins are commonly without valves and as noted earlier have rich communication with the vertebral veins.

Lung abscesses proverbially have secondary abscesses in the brain. The posterior bronchial vein and vertebral veins with the ever-present cough appear to present the plausible route of extension.

CONCLUSIONS

Many metastatic tumors and abscesses do not fit readily into accepted explanations for tumor spread. The absence of lung involvement has been a constant stumbling block to current theories. Even an open foramen ovale has been used to explain metastatic paradoxes.

The vertebral veins with their rich, valveless ramifications and connections offer a possible solution to the difficulty. Injections into this system by way of the deep dorsal vein of the penis gives a pattern duplicating typical prostatic carcinoma spread. Injection of breast venules seems to duplicate the pattern of aberrant breast cancer spread, *i.e.*, spread into the spine, the ribs, the shoulder girdle and the skull.

Injection experiments in living monkeys, with simulated abdominal straining, show that the venous flow from pelvic veins is into the vertebral vein system.

The vertebral vein complex with its cranial and body-wall connections acts as a separate vein system. It may be either a venous pool, or it may be a venous by-pass for the other vein systems.

It is possible to explain most cases of aberrant malignant metastases, aberrant pyogenic metastases and aberrant embolism following an injections by the demonstrated rôle of the vertebral vein system.

It is proposed that the veins of the brain, skull, neck, viscera, vertebral column (together with their valveless connections in the girdles) and the body-wall veins be considered a separate although overlapping, system of

veins We suggest, for brevity, that the term vertebral veins be used to indicate this system According to this concept the venous systems consist of the caval, pulmonary, portal and vertebral divisions

BIBLIOGRAPHY

- ¹ Warren S Harris, P N, and Graves, R C Osseous Metastasis of Carcinoma of the Prostate with Special Reference to Perineural Lymphatics Arch Path, **22**, 139-160 1936
- ² Batson O V Latex Emulsions in Human Vascular Preparations Science, **90**, 518-520, December 1, 1939
- ³ Hamilton, W F Woodbury, R A, and Hayser H T Physiologic Relationship between Intrathoracic Intraspinal and Arterial Pressures J A M A, **107**, 853-856, September 12, 1936
- ⁴ Handley, W S Cancer of the Breast and Its Treatment London, 1922
- ⁵ Willis, Rupert A The Spread of Tumors in the Human Body London, J & A Churchill p 321 1934
- ⁶ Walther, Hans E Untersuchungen uber Krebsmetastasen Ztschr f Krebsforsch, **46**, 313-333 1937
- ⁷ Breschet, Gilbert Recherches anatomiques physiologiques et pathologiques sur le systeme veineux Paris 1832
- ⁸ Franklin Kenneth I A Monograph on Veins Springfield, Charles C Thomas, p 77, 1937
- ⁹ Weirauch, H M, II Death from Air Embolism Following Perirenal Insufflation J A M A, **114**, 652-653 February 24, 1940
- ¹⁰ Walsh, F B, and Goldberg, H Krieger Blindness Due to Air Embolism A complication of Extrapleural Pneumolysis J A M A, **114**, 654, February 24, 1940
- ¹¹ Turner, John W, and Jaffe, Henry L Metastatic Neoplasms Amer Jour Roentgenol, **43**, 479-492, April, 1940
- ¹² Ormond, John K Fulminating Cancer of the Penis J A M A, **114**, 1546, April 20, 1940
- ¹³ Folsome, Clair E Benign and Malignant Tumors of the Vulva J A M A, **114**, 1499-1503, April 20, 1940

PLASMA TRANSFUSION IN THE TREATMENT OF THE FLUID SHIFT IN SEVERE BURNS

J RUSSELL ELKINTON, M D , WILLIAM A WOLFF, PH D ,

AND

WALTER ESTELL LEE, M D

PHILADELPHIA, PA

FROM THE SURGICAL SERVICES AND THE AYER CLINICAL LABORATORY OF THE PENNSYLVANIA HOSPITAL,
PHILADELPHIA, PA

THE MECHANISM and treatment of the fluid imbalance that occurs in severe burns is a special problem of surgical physiology. All too often, in discussions of fluid balance in surgical patients this problem is mentioned casually and therapy suggested that is definitely out of harmony with recent experimental findings on the subject. In the authors' opinion this situation warrants, at this time, further emphasis on the physiologic mechanism involved and its therapeutic implications.

Early reports from this clinic¹ have stressed the local treatment of burns. Recently, several cases of severe burns were observed in a study of the general problems of water and electrolyte control in surgical patients,^{2, 3} and these observations have led to a new interest in the pathologic physiology involved. Since that report appeared, five more cases of moderately severe burns have been observed. Plasma transfusion was studied as a treatment for the shift of body fluids that occurs during the first three days. An effort was made to quantitate the protein replacement and to determine the time at which the capillaries regain their impermeability to protein.

Physiologic Considerations—It has long been known that a decrease in the fluid fraction of the blood, variously termed as anhydremia, oligemia, or hemoconcentration, is a common phenomenon associated with severe burns. Baraduc,⁴ in 1862, described the thickening of the blood, and suggested that therapy should be directed toward the prevention of fluid loss from the burned surfaces and restoration of blood volume, especially the fluid part. Tappener,⁵ in 1881, and Locke,⁶ in 1902, reported the hemoconcentration of severe burns, and Underhill,⁷ in 1923, again emphasized its therapeutic and prognostic importance.

Experimental and clinical studies have done much to clarify the mechanism of this hemoconcentration. Davidson,⁸ in 1927, studied the plasma protein in ten cases and found a moderate lowering of the plasma protein concentration in the more severe cases, which finding, in the presence of hemoconcentration, was evidence of loss of whole plasma. Underhill, Kapsinow, and Fisk,⁹ in 1930, showed in experimental animals that the capillaries in the burned area were readily permeable to methylene blue and trypan blue, and that in a burn of one-sixth of the body surface, the local edema fluid was

equal to 70 per cent of the total blood volume, and, finally, that the composition of the local edema fluid closely resembled that of blood plasma. Blalock^{10, 11} found, in an experimental study, that the edema fluid accumulating in the burned area averaged 57 per cent of the total plasma volume and contained about the same concentration of protein as the plasma. McIver,¹² in a study of 16 patients stressed the loss of plasma as shown by a fall in the plasma level and hemoconcentration. Harkins^{13, 14} demonstrated in dogs a considerable reduction in "bleeding volume," and hence in blood volume, confirmed Blalock's finding of a marked fluid shift to the burned area, and showed the decelerating rate of the fluid accumulation. Weiner, Rowlette, and Elman¹⁵ emphasized, from a study of 40 patients, the loss of plasma protein. Schievers¹⁶ demonstrated experimentally the loss of plasma protein into the tissues of the burned area which reduced the absolute quantity of circulating plasma protein, and showed by the carbon monoxide method the simultaneous diminution of blood volume. Lambiet and Driessens¹⁷ found by the Congo red method a similar reduction of plasma volume in burned dogs, and demonstrated a high concentration of protein in the edema fluid. Keeley, Gibson and Pijoan,¹⁸ using the "Evans blue" method, found in burned dogs a 21 to 60 per cent reduction in plasma volume.

These experimental and clinical observations indicate the fundamental mechanism of the fluid imbalance which occurs during the first few hours after a severe burn. Capillary stasis and altered permeability in the burned area permit passage of plasma protein across the capillary membrane with a corresponding disturbance of osmotic pressure relationships. As a result, tissue fluids are increased and the plasma volume is diminished. This fluid imbalance is *primarily an abnormal distribution, or shift, of fluid rather than an external loss*. Some fluid and protein is lost externally from the burned surface before tanning may be completed, but the amount must be small compared to that which accumulates in the tissues.

This conception leads to certain logical deductions regarding therapy. Clearly, the fluid lost from the vascular compartment to the tissues would best be returned by replacing the lost plasma protein. This would raise the plasma osmotic pressure to a value sufficient to restore and maintain the normal distribution of fluid between the intravascular and interstitial compartments. In such a restoration of the plasma protein two factors must be considered. First, the time at which the capillaries in the burned area regain their impermeability to protein, and second, the total quantity of protein required. Furthermore, where there is not a marked external loss of fluid, the need for water and electrolytes is moderate only, as the excess fluid in the tissues should be available when the plasma osmotic pressure is restored to a normal level. The administration of excessive amounts of physiologic saline solution, without plasma protein, only increases an edema already present, and must be given in dangerously large amounts to have any significant effect on the plasma volume. The administration of large amounts of water alone, without sodium salts, may result in a dangerous lowering of the extracellular

electrolyte concentration, or water intoxication. This occurs because the lowered plasma volume and plasma protein concentration interfere with the normal renal defense by diuresis.

These ideas regarding therapy are not new. Riehl,¹⁹ in 1925, reported the beneficial effect of whole blood transfusion. Glover²⁰ pointed out the danger of producing a marked edema by the excessive use of saline infusions. The importance of replacing the lost plasma protein was fully appreciated by Weiner, Rowlette, and Elman¹⁵ who noted that in patients treated with large amounts of glucose and saline solutions alone there was a fall in plasma protein with little correction of the hemoconcentration. The latter authors obtained prompt correction of the hemoconcentration in a number of patients by the intravenous use of acacia or plasma, and pointed out that "plasma is apparently more efficacious than whole blood because of the excessive concentration of red blood cells already present." Wilson, MacGiegor, and Stewart²¹ used intravenous gum acacia-saline and whole blood in their series of cases with great success. On the basis of experimental and clinical observations McClure²² has advocated the prompt replacement of circulating protein by plasma transfusions. Trusler, Egbert, and Williams²³ have also employed whole blood and plasma transfusions and have cautioned against the possibility of water intoxication resulting from the excess use of fluids. Plasma transfusion combined with fluids in moderate amounts has already been stressed in publications from this clinic^{2, 3} as the logical treatment in burns.

Scudder²⁴ has advocated the employment of adrenal cortical extract and hypertonic saline solution, and showed, in one of his cases, that these agents apparently had a great effect on the plasma volume in the absence of either quantitative protein replacement or administration of excessive amounts of normal saline solution and water. Whether or not this regimen is better than the one employed here remains to be seen. But in the five cases reported in this paper, plasma transfusion was administered alone, in an effort to evaluate its therapeutic efficacy.

Method of Study—During the phase of fluid shift, hematocrit and plasma protein determinations were made every few hours. From these figures approximate plasma volumes and total amounts of circulating plasma protein were calculated. The amount of plasma corresponding to a unit volume of cells at any hematocrit value may be compared with the plasma corresponding to the unit volume of cells at the normal hematocrit value to give a ratio of plasma volume changes. This ratio is expressed as follows:

$$\frac{(100 - H_o) H_n}{(100 - H_n) H_o}$$

where H_n stands for the normal hematocrit value and H_o for the observed hematocrit value. When the normal plasma volume, arbitrarily assumed to equal 5 per cent of the body weight, is multiplied by this factor, an approximate value for the observed plasma volume is obtained. From this plasma volume, and the observed plasma protein concentration, the total amount of

circulating plasma protein is estimated. The plasma deficit is the difference between the latter value and the normal total amount of plasma protein (7 Gm per cent times the normal plasma volume)

The derivation of these values at a given time may be illustrated as follows

Normal body weight (W)	= 79 Kg
Normal hematocrit (Hn)	= 44% cells
Normal plasma volume	= $0.05 \times 79 = 3.95$ liters
Normal total amount of plasma protein	= $70 \times 3.95 = 276$ Gm
Normal plasma protein conc (Pn)	= 7 Gm per cent
Observed hematocrit (Ho)	= 57% cells
Observed plasma protein conc (Po)	= 6.4 Gm per cent
Observed plasma volume	= $\frac{(100 - H_o) H_n}{(100 - H_n) H_o} \times \text{normal plasma volume} =$

$$\frac{43 \times 44 \times 3.95}{56 \times 57} = 2.34 \text{ liters} = 59\% \text{ of normal}$$

Observed total amount of plasma protein	= $6.4 \times 2.34 = 150$ Gm = 54% of normal
Plasma protein deficit	= $276 - 150 = 126$ Gm

This calculation of the plasma protein deficit may be expressed in a single formula as follows

$$\text{Plasma protein deficit in grams} = 3.5 W - \frac{W (100 - H_o) H_n P_o}{2 (100 - H_n) H_o}$$

The deficit, or requirement in grams of protein, may be converted into cubic centimeters of plasma by multiplication by the factor 14

Such a calculation of the deficit involves the errors inherent in the measurement of hematocrit and plasma protein values and in the assumption of normal hematocrit level and plasma volume. These errors may be cumulative, and the final result is an approximation only. However, in the cases reported herewith, the calculated requirement should be within 10 per cent of the real value.

Patients were followed in this manner during the first 72 hours after the burn. Plasma protein was supplied in the form of plasma transfusions. These were given at various time intervals after the burn in order to determine the ability of the capillaries to hold protein. Fluids were given in various amounts, the urinary output was measured, and the insensible loss of water was estimated.

The plasma employed in the transfusions was obtained by centrifuging citrated whole blood. Some of this was routinely separated from five-day-old blood in the Blood Bank. The remainder was separated from freshly drawn blood. Plasma was pooled from any type of blood available and no reactions were observed. It was given undiluted in order to obtain the maximum osmotic effect.

CASE REPORTS

Case 5^{*}—C. E., Negro, male, age 33, sustained, from boiling water, second and third degree burns of left side of the chest, abdomen, and back from midline anteriorly to

^{*} Cases 1 to 4 (inclusive) of this series have been reported^{2, 3}

midline posteriorly, left upper arm, right hand, and left thigh (25 per cent of the body surface) Treated locally with 10 per cent tannic acid and 10 per cent silver nitrate

Mild local edema first four days Systemic reaction with fever, albuminuria, and impairment of liver function reaching a peak on fifth and sixth days Eschar completely removed between eighth and fifteenth days Mercresin and saline soaks to granulating areas with several skin graftings Discharged healed on one hundred fourteenth day

Chart 1—Case 5 shows

(1) The immediate loss of plasma volume to 63 per cent of normal within 40 minutes after the burn

(2) The corresponding rapid loss of plasma protein

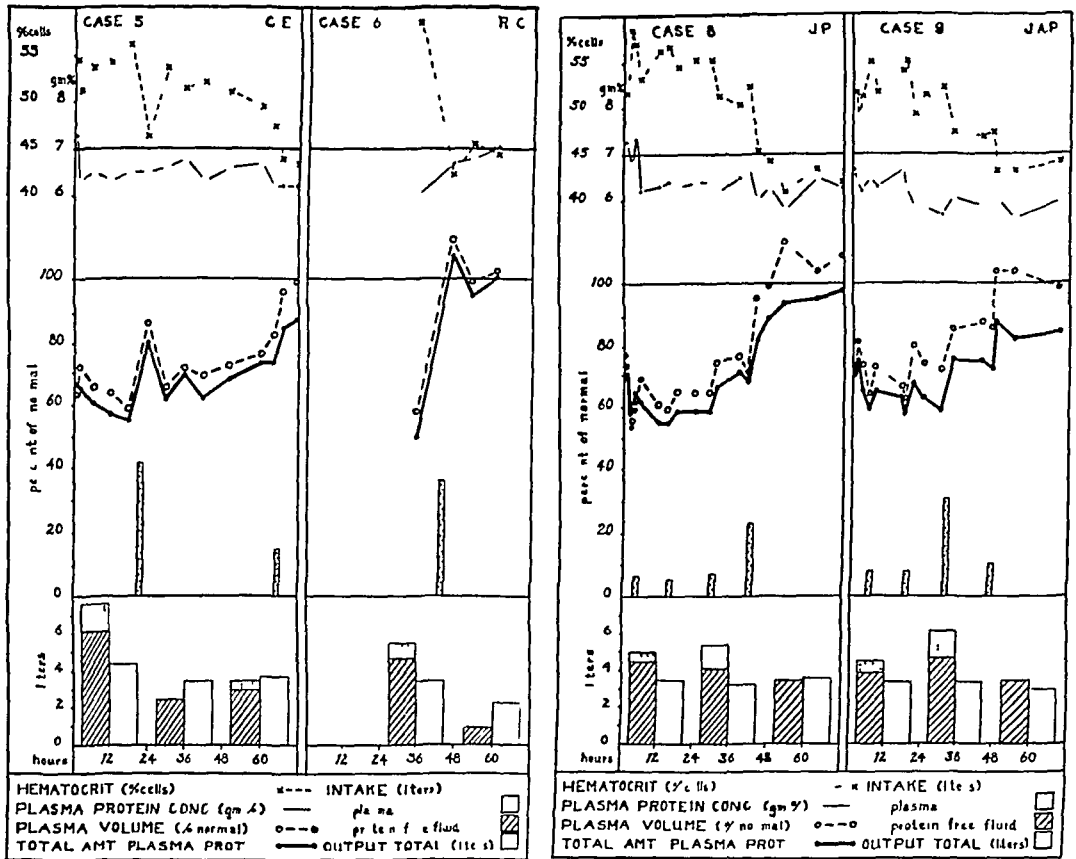


CHART 1—Case 5

CHART 1—Case 6

CHART 2—Case 8

CHART 2—Case 9

(3) The lack of effect on the plasma volume of the administration of 6,000 cc of protein-free fluids during the first 24 hours

(4) The immediate response of the plasma volume to the plasma transfusion of 1,400 cc during the twenty-first and twenty-second hours

(5) The loss of most of this administered plasma protein within six hours, and the corresponding drop in plasma volume

(6) The plasma transfusion during the sixty-sixth hour, returning the plasma volume approximately to normal

(7) The restoration of plasma volume without a positive water balance of protein-free fluid

Case 6—R C, Puerto Rican, male, age 37, sustained, from boiling water, second degree burns of lower chest and abdomen, left thigh, and left forearm (10 per cent of body surface) Admitted 24 hours after burn occurred Treated locally with 10 per cent tannic acid and 10 per cent silver nitrate

No local edema No systemic reaction except for albuminuria on fifth day Primary healing under eschar Discharged healed on thirty-ninth day after the burn

Chart 1—Case 6 shows

(1) The marked loss of plasma volume and total amount of circulating plasma protein that may occur with a relatively small burn that is neglected

(2) The prompt, adequate response to plasma transfusion given during forty-fourth and forty-fifth hours after burn

(3) The ability of capillaries to hold protein at this time

(4) The restoration of plasma volume without a positive water balance of protein-free fluid

Case 7—P C, white, male, age 60, sustained, from boiling water, first and second degree burns of scalp, face, neck and shoulders (10 per cent of body surface) Treated locally with 2 per cent gentian violet

Moderate local edema first ten days No systemic reaction Primary healing under eschar Discharged fourteenth day

No chart is shown because the changes were qualitatively identical with those shown in the other cases However, the following facts are presented

(1) The plasma volume fell to 82 per cent of normal at one hour after the burn, and reached its lowest value, 75 per cent of normal, at 18 hours

(2) There was a corresponding fall in total amount of circulating plasma protein

(3) There was a return of plasma volume to normal following a plasma transfusion of 580 cc during the fortieth hour

(4) The capillaries held this protein, given during the fortieth hour

Case 8—J P, Negro, male, age 44 sustained, from fire, second and third degree burns of face, neck, forearms and hands (15 per cent of body surface) Treated locally with 2 per cent gentian violet

Severe edema at sites of burn during first three days Marked systemic disturbance with fever, albuminuria, impairment of liver function Severe irritative bronchitis from smoke inhalation Hemolytic streptococcus isolated on the fifth day from under eschar, which had not been completely removed Despite sulfanilamide, developed septicemia and died, acutely febrile, on eighth day

Chart 2—Case 8 shows

(1) The extremely rapid diminution of plasma volume to 73 per cent of normal in 15 minutes after the burn, and to 55 per cent in three hours

(2) The corresponding rapid loss of plasma protein

(3) The administration of small doses of protein in plasma transfusion to prevent excessive hemoconcentration, until the capillaries regained their impermeability to protein

(4) The administration of a large plasma transfusion during the forty-first and forty-second hours, with an adequate rise in plasma volume and retention of plasma protein

(5) The restoration of plasma volume without a large positive water balance of protein-free fluid

Case 9—J A P, white, male, age 23, sustained, from fire, second and third degree burns of the right shoulder, upper arm, back, side, chest, upper abdomen, and left hand (20 per cent of the body surface) Treated locally with 2 per cent gentian violet

Severe edema of burned areas during first seven days Systemic reaction with albuminuria, fever, impaired liver function Areas of local infection, with eschar completely removed twelfth to fifteenth day Mercresin and saline soaks to granulating areas, and skin grafts Discharged practically healed on seventy-eighth day

Chart 2—Case 9 shows

(1) The initial rapid diminution of plasma volume to 73 per cent of normal in 20 minutes after the burn

(2) The corresponding rapid loss of plasma protein

(3) The administration of small doses of protein in plasma transfusion to prevent excessive hemoconcentration

(4) The administration of a large amount of protein during the thirty-first and thirty-second hours, with only partial restoration of plasma volume and partial retention of plasma protein

(5) The complete restoration of plasma volume, with final small dose of protein given during forty-seventh hour

(6) The restoration of plasma volume without a large positive water balance of protein-free fluid

SUMMARY AND CONCLUSIONS

Five cases of moderately severe burns have been studied in the light of recent experimental and clinical observations. The results are in accordance with the view that the fluid imbalance is primarily due to an altered capillary permeability with a shift of fluid and protein into the tissues, rather than an external loss.

The restoration of plasma protein by means of plasma transfusion is a rational treatment for this fluid shift.

Evidence is presented that the loss of plasma protein continues until the thirty-first to fortieth hour. During this period excessive hemoconcentration may be prevented by small repeated plasma transfusions. Whether or not this period of healing is a general biologic property of damaged capillaries cannot be stated from the evidence at hand.

After the fortieth hour, when the capillaries have regained their impermeability to protein, the deficit of plasma protein may be corrected, quantitatively, by a large plasma transfusion. The amount of protein required is calculated by a formula based on hematocrit values, plasma protein concentration, and body weight.

This regimen permits the restoration of plasma volume to normal without the administration of excessive amounts of protein-free fluids.

The authors are indebted to Dr. John B. Flick for access to patients on his Service, and acknowledge the assistance of the hospital clinical and laboratory staffs.

REFERENCES

- ¹ Lee, W. E. Surgical Treatment of Burns. *Therap. Gaz.*, **44**, 685, 1920.
- ² Elkinton, J. R., Gilmour, M. T., and Wolff, W. A. The Control of Water and Electrolyte Balance in Surgical Patients. *ANNALS OF SURGERY*, **110**, 1050, 1939.
- ³ Elkinton, J. R. The Systemic Disturbances in Severe Burns and Their Treatment. *Bull. Ayer Clin. Lab., Pennsylvania Hosp.*, **3**, 279, 1939.
- ⁴ Bardauc, H. Des Causes de la Mort à la suite des Brûlures Superficielles, de Moyens de l'éviter. Paris, 1862.
- ⁵ Tappener, H. Über Veränderungen des Blutes und der Muskeln nach ausgedehnten Hautverbrennungen. *Centralbl. f. d. med. Wiss.*, **19**, 385, 401, 1881.
- ⁶ Locke, E. H. A Report of the Blood Examination in Ten Cases of Severe Burns of the Skin. *Boston Med. and Surg. Jour.*, **147**, 480, 1902.
- ⁷ Underhill, F. P., Carrington, G. L., Kapsinow, R., and Pack, G. T. Blood Concentration Changes in Extensive Superficial Burns, and Their Significance for Systemic Treatment. *Arch. Int. Med.*, **32**, 31, 1923.
- ⁸ Davidson, E. C., and Matthew, C. W. Plasma Proteins in Cutaneous Burns. *Arch. Surg.*, **15**, 265, 1927.
- ⁹ Underhill, F. P., Kapsinow, R., and Fisk, M. E. Studies on Mechanism of Water

- Exchange Induced by Superficial Burns Amer Jour Physiol, 95, 315, 325, 334, 339, 1930
- ¹⁰ Blalock, A Experimental Shock VII The Importance of the Local Loss of Fluid in the Production of the Low Blood Pressure after Burns Arch Surg, 22, 610, 1931
- ¹¹ Beard, J W, and Blalock, A Experimental Shock VIII The Composition of the Fluid That Escapes from the Blood Stream after Mild Trauma to an Extremity, after Trauma to the Intestines, and after Burns Arch Surg, 22, 617, 1931
- ¹² McIver, M A A Study in Extensive Cutaneous Burns ANNALS OF SURGERY, 97, 670, 1933
- ¹³ Harkins, H N Experimental Burns I The Rate of Fluid Shift and Its Relation to the Onset of Shock in Severe Burns Arch Surg, 31, 71, 1935
- ¹⁴ Harkins, H N The Bleeding Volume in Severe Burns ANNALS OF SURGERY, 102, 444 1935
- ¹⁵ Weiner, D O, Rowlette A P, and Elman, R The Significance of Loss of Serum Protein in Therapy of Severe Burns Proc Soc Exper Biol and Med, 34, 484, 1936
- ¹⁶ Schievers, J Le Volume Sanguin apres Brûlure Étendue Arch internat de pharmacodyn et de therap, 52, 452, 1936
- ¹⁷ Lambret, O, and Driessens I Le Syndrome Humoro-tissulaire des Brûlures Étendues Pathogenie Traitement Rev de chir, Paris, 76, 319, 1937
- ¹⁸ Keeley, J L, Gibson, J G and Pijoan, M The Effect of Thermal Trauma on Blood Volume, Serum Protein and Certain Blood Electrolytes An Experimental Study of the Effect of Burns Surgery, 5, 872, 1939
- ¹⁹ Riehl, G Treatment of Severe Burns by Blood Transfusion Wien klin Wchnschr, 38, 833, 1925 (Abst J A M A 85, 860, 1925)
- ²⁰ Glover, D M Six Years of Tannic Acid Treatment of Burns Surg, Gynec and Obstet, 54, 798, 1932
- ²¹ Wilson, W C MacGregor, A R, and Stewart, C P Clinical Course and Pathology of Burns and Scalds under Modern Methods of Treatment Brit Jour Surg, 25, 826, 1938
- ²² McClure, R D The Treatment of the Patient with Severe Burns J A M A, 113, 1808, 1939
- ²³ Trusler, H M, Egbert, H L, and Williams, H S Burns Shock Water Intoxication as a Complication J A M A, 113, 2207, 1939
- ²⁴ Scudder, J Shock Blood Studies as a Guide to Therapy J B Lippincott Co, Philadelphia, 1940

LIVER DAMAGE AND DEXTROSE TOLERANCE IN SEVERE BURNS

WILLIAM A. WOLFF, PH D, J. RUSSELL ELKINTON, M D,

AND

JONATHAN E. RHOADS, M D

PHILADELPHIA, PA

FROM THE AYER CLINICAL LABORATORY AND THE SURGICAL SERVICES OF THE PENNSYLVANIA HOSPITAL,
PHILADELPHIA, PA

Information concerning damage to the liver in patients with severe burns has been based in the past, largely, on histologic studies of postmortem material¹. In the present study, objective evidence of hepatic damage was obtained during life by the use of liver function tests. Three patients with second and third degree burns of 15 to 25 per cent of the body surface were studied. Details of the case histories have been published elsewhere². Disturbances in the fluid balance of these patients were corrected within 48 hours after the burn by the employment of plasma transfusions, and at no time did the patients show marked symptoms of secondary shock. Cases 5 and 9 recovered while Case 8 died with a hemolytic streptococcal septicemia, on the eighth day.

Bilirubinemia, bromsulphalein retention, hippuric acid output, plasma prothrombin concentration and dextrose tolerance were determined in the three cases at frequent intervals. The results are presented in Charts 1, 2 and 3. The hyperbilirubinemia, during the first 48 hours, may have been caused either by a rapid breakdown of red cells injured by heat in the burned area, or by failure of the liver to excrete bilirubin at a normal rate. An abnormal bromsulphalein retention was observed between the fourth and fifteenth days of each case. During this period, the capacity of the liver for producing glycine and forming hippuric acid became impaired to a variable extent in Cases 8 and 9, an observation which confirms the report of Boyce and McFetridge³. Moderate reductions in the plasma prothrombin concentration were observed in each case. As none of the other causes of hypoprothrombinemia were present, this finding may be regarded as presumptive evidence of hepatic damage.

The dextrose tolerance curve is the result of several factors, of which the functional capacity of the liver is one. Curves obtained on these patients show marked deviations from the normal. Although the curves might be regarded as evidence for impairment of the hepatic mechanism for glycogenesis, other factors, hormonal and dietary, must be evaluated before an accurate interpretation can be made.

LIVER DAMAGE IN BURNS

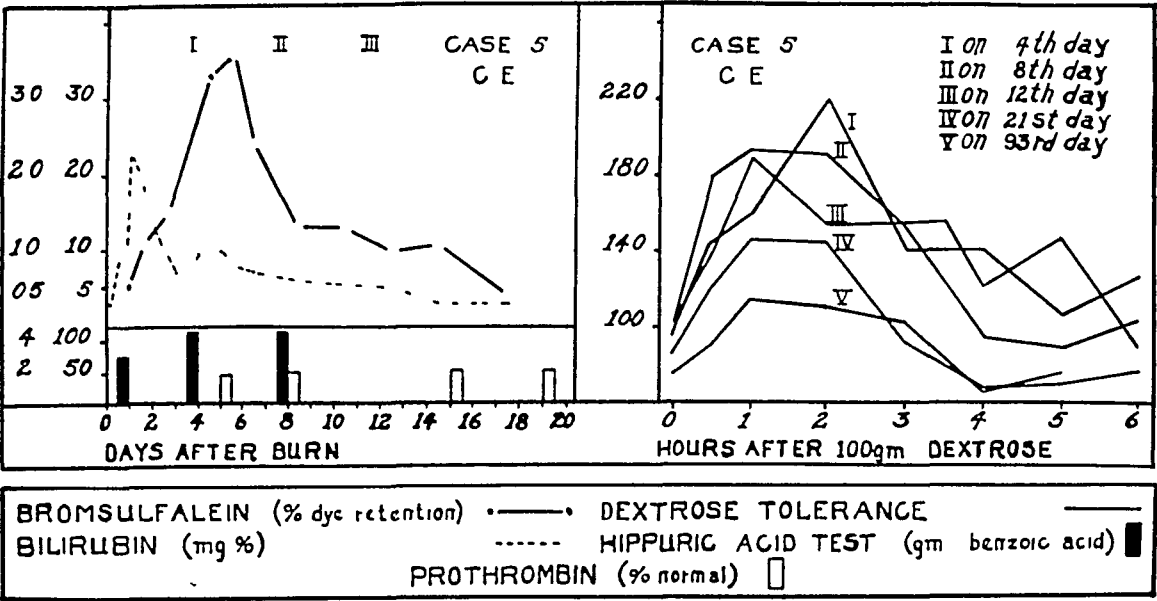


CHART 1, Case 5

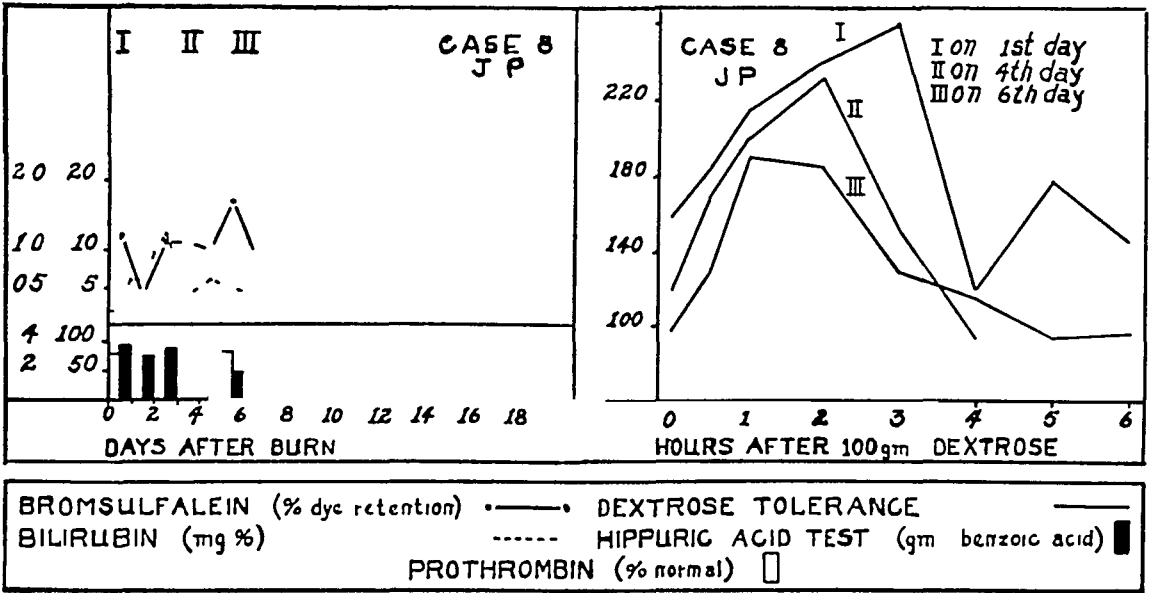


CHART 2, Case 8

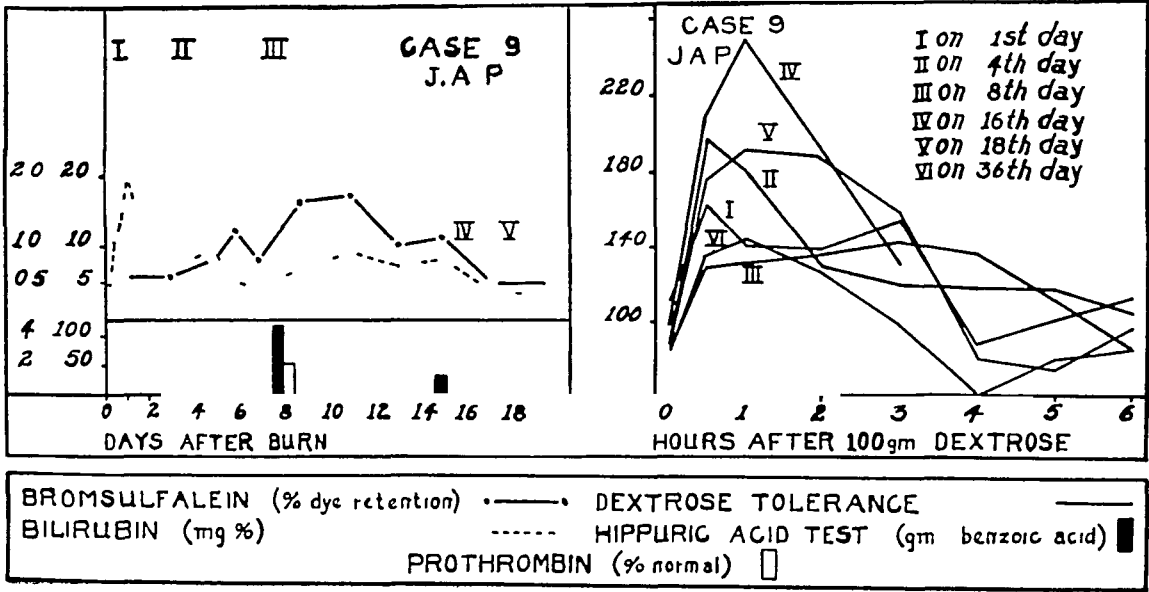


CHART 3, Case 9

CONCLUSIONS

The effect of severe burns on bilirubinemia, bromsulphalein retention, hippuric acid formation, prothrombinemia, and dextrose tolerance were studied in three patients. The changes found in bromsulphalein retention, hippuric acid formation, and prothrombinemia indicate the presence of hepatic damage, especially during the period from the third to the tenth day following the injury. The changes in the bilirubin and dextrose tolerance are also suggestive of liver injury. Whether the cause of the disturbance in the liver is a toxin from the burned area, anoxia associated with capillary stasis, infection, or a combination of these factors cannot be stated at the present time.

REFERENCES

- ¹ Wilson, W. C., MacGiegor, A. R., and Stewart, C. P. The Clinical Course and Pathology of Burns and Scalds under Modern Methods of Treatment. *Brit Jour Surg*, 25, 826, 1938.
- ² Elkinton, J. R., Wolff, W. A., and Lee, W. E. Plasma Transfusion in the Treatment of the Fluid Shift in Severe Burns. *ANNALS OF SURGERY*, 112, 150, July, 1940.
- ³ Boyce, F. F., and McFetridge, E. M. Studies of Hepatic Function by Quick Hippuric Acid Test, Various Surgical States. *Arch Surg*, 37, 443, 1938.

ERRATUM

In the article by Dr. Charles H. Watt, "A Modified Spur-Crushing Clamp and Its Use," appearing in the *ANNALS OF SURGERY*, 111, 1076-1083, June, 1940, the legend for Figure 1 should read "The author's modification of the Stetten spur-crusher. The original Stetten clamp does not have the blade."

EDITORIAL ADDRESS

Original typed manuscripts and illustrations submitted to this Journal should be forwarded prepaid, at the author's risk, to the Chairman of the Editorial Board of the *ANNALS OF SURGERY*.

Walter Estell Lee, M.D.
1833 Pine Street, Philadelphia, Pa.

Contributions in a foreign language when accepted will be translated and published in English.

Exchanges and Books for Review should be sent to James T. Pilcher, M.D., Managing Editor, 121 Gates Avenue, Brooklyn, N.Y.

Subscriptions, advertising and all business communications should be addressed

ANNALS OF SURGERY
227 South Sixth Street, Philadelphia, Pa.



TUMORS OF ISLET CELLS WITH HYPERINSULINISM, BENIGN, MALIGNANT, AND QUESTIONABLE

V KNEELAND FRANTZ, M D

NEW YORK, N Y

FROM THE SURGICAL PATHOLOGY LABORATORY OF THE COLLEGE OF PHYSICIANS AND SURGEONS, COLUMBIA UNIVERSITY, AND THE DEPARTMENT OF SURGERY, PRESBYTERIAN HOSPITAL, NEW YORK, N Y

AS THE NUMBER of reported cases of hypoglycemia with islet cell tumor increases, one is struck in reviewing the literature by the large proportion of circumscribed tumors removed with relief of symptoms in which the pathologist has been in doubt as to whether the tumor was malignant or benign. The most notable case in point is the first successful operative removal by Roscoe Graham, in 1929, of a tumor thought possibly malignant, reported by Howland, Campbell, Maltby and Robinson¹⁷ (1929). The ten-year follow-up on this case has recently been published by Campbell, Graham and Robinson¹³ (1939).

In our own series (Whipple and Frantz,⁸¹ 1935) of eight tumors in six patients, no tumor had seemed to us to have any features suggestive of malignancy, microscopically, other than lack of complete encapsulation. Since then, however, in subsequent cases in our series, the histologic findings in some were definitely suggestive of malignancy. Some of these were listed by Whipple⁸⁰ (1938) but without pathologic report. It is the purpose of this paper to present these in greater detail and to analyze the cases reported in the literature to date (December 31, 1939), as far as it has been possible to find them,* with particular reference to possible malignant characteristics †

To date (December 31, 1939), in this hospital, 16 patients have been explored because of hypoglycemia. In one case, no tumor was found and partial pancreatectomy was performed with some relief. In the 15 cases with tumor, three had two tumors, making a total of 18 tumors for examination. Of these, four showed lack of encapsulation and blood vessel invasion, leading us to fear that they were malignant.

Submitted for publication February 2, 1940

* The Quarterly Index, at the time this is submitted for publication, is available only through September, 1939.

† The tables and the discussion which follow are limited to those cases in which there were hypoglycemia and islet cell tumor. This necessitates eliminating the following cases, some of which have occasionally been misquoted: Vecchi,⁷⁷ 1914, Zanetti,⁸⁷ 1927, Fahri and Sedad,²⁰ 1929, Fedoroff,²¹ 1931, Hamdi,³⁰ 1932, Cottalorda and Escarras,¹⁵ 1933, Berardinelli,⁷ 1934, Herman,³⁴ 1935, Evangelisti,¹⁹ 1935, Bailey and Cutler,³ 1938, Dubois-Ferriere,¹⁸ 1939.

ABBREVIATED CASE REPORTS OF FOUR INSTANCES OF ISLET CELL TUMOR
THOUGHT POSSIBLY TO BE MALIGNANT

Case 1—Whipple,⁸⁰ Case 8 (1938) Presbyterian Hospital No 510933 A M, white, male, age 51 Symptoms for one year, characterized by inability to be roused in the early morning, irrationality, psychomotor activity, and amnesia for the attacks Patient noted food relationship and for six months before admission had been taking sugar and orange



FIG 1—Case 1 Low power photomicrograph showing circumscribed tumor and adjacent pancreas The capsule microscopically however was not complete Note the fibrosis in the tumor

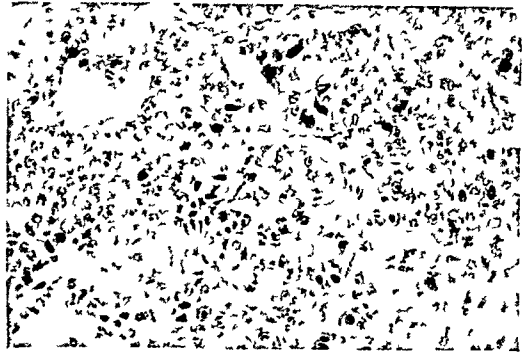


FIG 2—Case 1 Higher power photomicrograph showing arrangement of tumor cells, notably around vascular spaces The cells show some pleomorphism but the tumor is well differentiated

juice at bedtime and at 4 A M Attacks increasing in frequency Minimum blood sugar 37 mg per cent

Operation—February 4, 1937 Dr Allen O Whipple No tumor found at first and, therefore, the tail and half of the body were resected It was then possible to palpate the tumor in the head, and shell it out

Postoperative Course—Patient improved for first 36 hours, stated that he felt men-

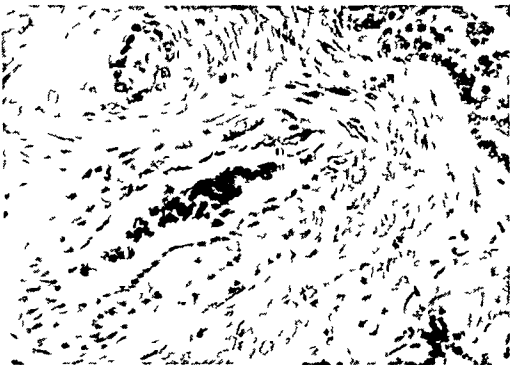


FIG 3

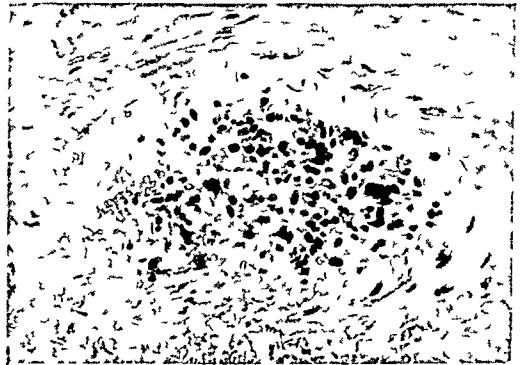


FIG 4

FIGS 3 and 4—Case 1 Photomicrographs showing tumor cells in blood vessels

tally clearer, and had no further hypoglycemia But he developed bronchopneumonia and died, his temperature rising to 108° F, and his blood amylase to 138 units (Myers and Kilian method) No autopsy was obtained

Pathologic Examination—Gross Path No 63130, Dr V K Frantz The tumor, apparently encapsulated, measured 1.5 x 1.0 x 0.8 cm, and had a thin strip of pancreatic tissue adherent to the capsule It appeared yellowish, with a faint bluish overtone, and the surface vessels were fine but engorged On section, it was soft, pinkish-yellow, with ill-defined areas of white fibrous tissue

Microscopically (Figs 1, 2, 3 and 4), the capsule was incomplete, tumor cells appeared to invade the surrounding pancreas The cells, which somewhat resembled the cells of the islands in the adjacent pancreas, were arranged in ribbon-like cords, sometimes

arranged in rosettes about endothelial-lined blood-filled spaces, or about similar spaces lacking an endothelial lining. There was considerable variation in cell size and quite marked hyperchromatism. No mitoses were seen.

Dr Margaret Murray attempted to cultivate this tumor *in vitro*, but failed, although she had previously obtained excellent growth from an islet cell adenoma, with subsequent graft into a diabetic patient (Murray and Bradley,⁶⁰ 1935).

Case 2—Whipple,⁸⁰ Case 10 (1938) Presbyterian Hospital No 540606 J S, white, male age 50. Symptoms for one year, characterized by attacks of confusion, disorientation, and unconsciousness with convulsive movements, with amnesia for the attacks. The episodes occurred chiefly during the early morning. For four months before admission they had increased in frequency and severity. The minimum blood sugar 27 mg per cent.

Operation—January 13, 1938. Dr Allen O Whipple. Splenectomy and resection of the tail of the pancreas, in which a tumor was palpable.

Subsequent Course—Patient made good recovery from operation and is free from evidence of disease, 17 months later.

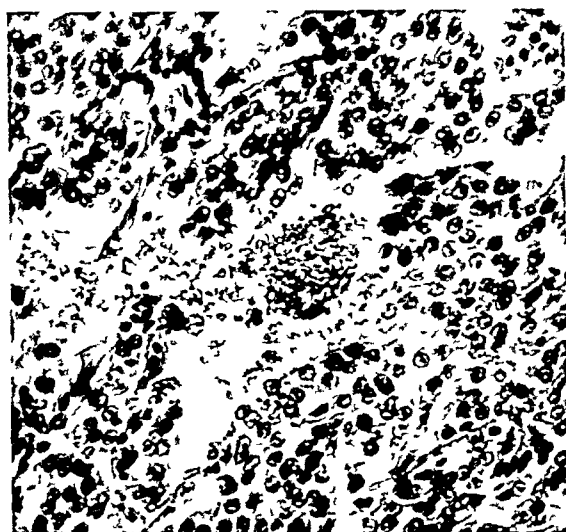


FIG 5—Case 2. Photomicrograph showing the general topography of the tumor. Note the large number of vascular spaces, and moderate variability in the cells.

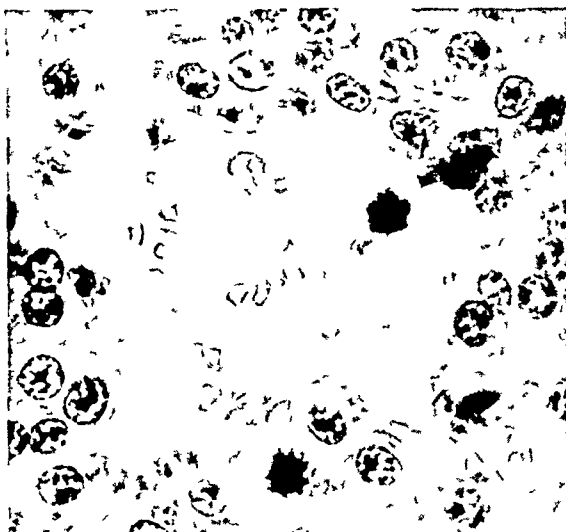


FIG 6—Case 2. Higher power photomicrograph showing a vascular space lined by tumor cells, with cells in mitosis bordering the lumen, and one in mitosis, free in the lumen among the erythrocytes.

Pathologic Examination—Gross. Path No 66090, Dr V K Frantz. On the anterior aspect of the specimen of tail of the pancreas submitted, there was a bluish swelling shining through the capsule of the gland. On section, this proved to be an oval, almost completely encapsulated mass of very friable, very soft, dark-purplish tissue. The encapsulation, grossly, was not complete over one small area.

Microscopically (Figs 5 and 6), the capsule was incomplete. The tumor was composed of cells resembling the cells of the islet tissue in the adjacent pancreas. There were occasionally, however, much larger cells, and numerous mitotic figures. The cells were arranged in broad, wavy bands, separated from one another by irregular spaces filled with blood. Only occasionally could an endothelial lining be observed in these spaces. In at least four instances, cells in mitosis were found directly lining a vascular space, and, in two instances, a cell in mitosis lay free in one of the vascular spaces.

Dr Margaret Murray cultivated this tumor *in vitro* (Figs 7 and 8). The growth was much more vigorous than in the tumors previously cultivated and more bizarre. The first epithelial growth was observed in 24 hours, the shortest latent period of any of the tumors. By the fourth day, there was a diffuse growth in most of the cultures. There was some pleomorphism. A striking feature of the first growth was the appearance of large multinucleated cells. These did not reappear after the cultures were transferred. The rapidity of cell multiplication approached the rate of growth of embryonic tissue. Mitoses averaged six to a culture, at any given time.

Case 3—Whipple, Case 12 (not yet published) Presbyterian Hospital No 546637 M O, white, female, age 20 Episodes of fatigue, confusion and dizziness since childhood A year before admission, attacks of confusion often with complete amnesia usually occurring on awakening, lasting from six to eight hours No attacks occurred after meals, and relief was obtained by taking orange juice Minimum blood sugar 26 mg per cent

Operation—April 30, 1938 Dr Allen O Whipple An adenoma was found on the



FIG 7—Case 2 Photomicrograph of the tissue culture showing epithelium not of the pavement type

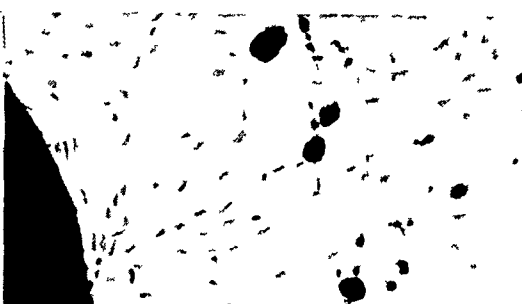


FIG 8—Case 2 Photomicrograph of the tissue culture showing multinucleated cells in the first outgrowth

anterior surface of the body of the pancreas near the lower border This was easily shelled out

Subsequent Course—The patient made a good recovery, and was symptom-free, 13 months after operation

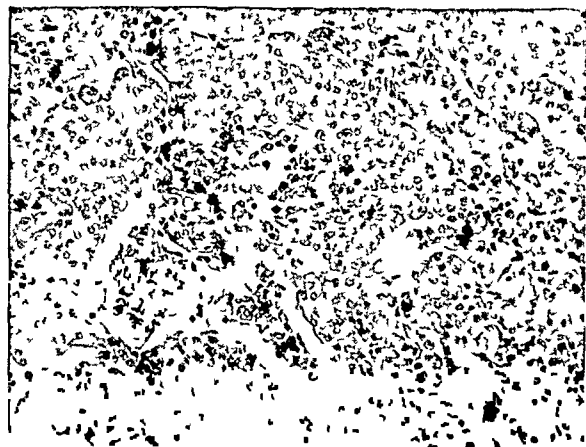


FIG 9—Case 3 Photomicrograph of the general topography showing ribbon like arrangement of tumor and many vascular spaces

the islands of the adjacent pancreas They were slightly larger and the cell outlines were indistinct They were arranged in ribbon-like, winding cords interspersed with capillary spaces (Fig 9) There were also many blood-filled spaces directly lined by tumor cells No mitotic figures were seen Many of the large blood vessels contained clumps of tumor cells

This tumor was not cultivated *in vitro*

Case 4—Whipple, Case 15 (not yet published) Presbyterian Hospital No 583832 O A, white, male, age 46 Symptoms for four years, characterized by fainting spells and amnesia before attacks The episodes started with blurred vision and dizziness, and the patient noted that exercise precipitated them but did not note any relation to food No unusual psychiatric behavior and no convulsions Minimum blood sugar 36 mg per cent The patient had been explored one year before admission in another hospital No tumor was found and no part of the pancreas resected During the year following operation, he

Pathologic Examination—Gross

Path No 67137, Dr V K Frantz The tumor, apparently encapsulated, was biscuit-shaped, and measured 1.2 cm in greatest diameter A small strip of pancreatic tissue was attached The tumor was soft and reddish On section, under about one-third of the capsule there was yellowish tissue, suggesting pancreas The rest of the mass was composed of homogeneous, soft, pinkish-yellow tissue apparently more vascular in the center

Microscopically, the capsule was incomplete and tumor tissue mingled with pancreatic tissue in a portion of the periphery The tumor was composed of cells resembling the cells in

was considerably benefited by a high carbohydrate diet, with seven meals a day, which resulted in a gain of 18 pounds

Operation—June 27, 1939 Dr Allen O Whipple After mobilizing the duodenum and the head of the pancreas, the adenoma was found in the posterior portion of the pan-

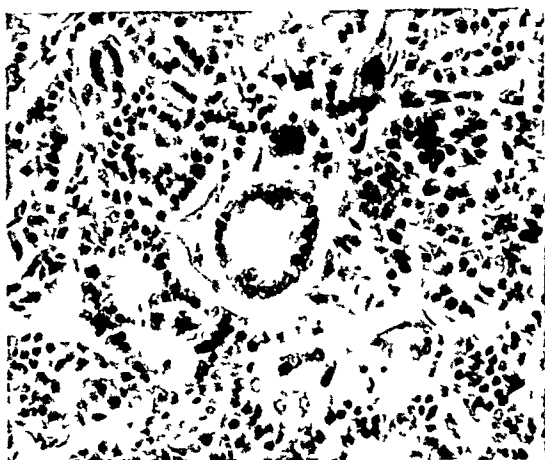


FIG 10—Case 4. Photomicrograph of the general topography showing good differentiation, occasional ducts, and many vascular spaces

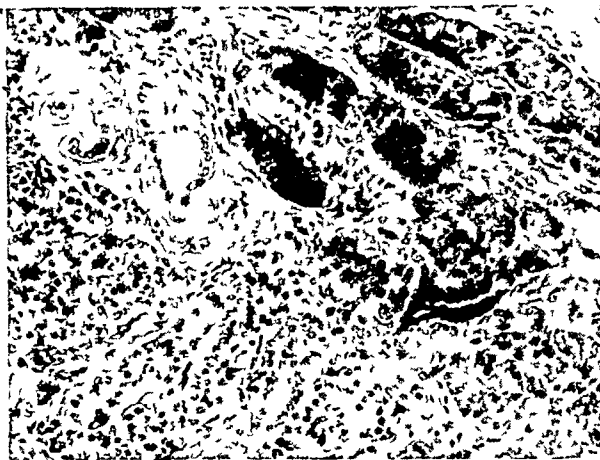


FIG 11—Case 4. Photomicrograph of the tumor and adjacent pancreas showing lack of encapsulation

creas near the lower border, between the superior mesenteric vessels on the mesial aspect and the inferior pancreaticoduodenal vessels on the right

Subsequent Course—Patient made a good recovery, and was symptom-free, five months after operation

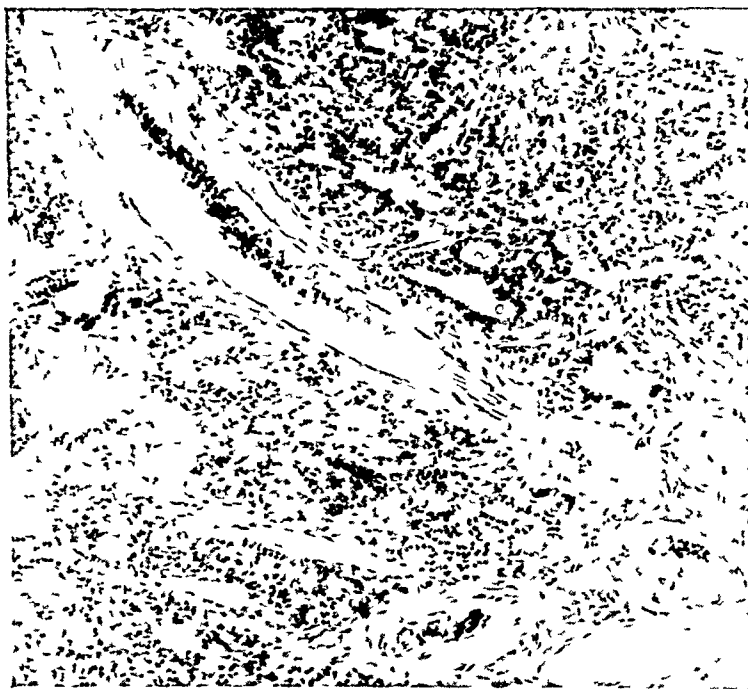


FIG 12—Case 4. Photomicrograph showing tumor cells in three different sections of blood vessels

Pathologic Examination—Gross Path No 71155, Dr A P Stout The tumor was irregularly rounded, apparently encapsulated, and dark-pink, measuring 1.5 cm in greatest diameter. Adherent to the surface of the capsule there was a small amount of pancreatic tissue. On section, the cut surface was soft, delicately homogeneous, and mottled by various shades of red and pink.

Microscopically (Figs 10, 11 and 12), the tumor, in general, was separated from the pancreatic tissue by a delicate capsule but in a few areas tumor cells appeared to be in

contact with the acinar cells. The tumor was composed of cells resembling those of the normal pancreatic islands. They formed anastomosing cords supported by bands of fibrous tissue in which there were many blood vessels, chiefly capillaries. Occasionally ducts were seen in the tumor. In some of the larger blood vessels masses of what appeared to be degenerated tumor cells were found within the lumen.

No attempt was made to cultivate this tumor *in vitro*.

These four cases have been a great puzzle to us. The postoperative mortality in the first case, in which no autopsy was obtained, left no possibility of further investigation of the nature of the tumor. The second case had all the appearance of a carcinoma microscopically. This patient, in spite of our apprehension, has remained well for 17 months. The last two cases, which appeared less malignant than the second, but which had blood vessel invasion, are symptom-free, 13 and five months, respectively.

There can be no dispute about the malignancy in five published cases of hypoglycemia in which carcinoma of islet cells with metastases was found. It is noteworthy that these were all fulminating cases of short duration. It is also of interest that metastases were found at autopsy in the liver, the lymph nodes, mesentery, peritoneum and epicardium, but not elsewhere. There can be little doubt of the functional nature of the metastases, as illustrated by the

TABLE I

HYPOGLYCEMIA ISLET CELL TUMORS IN WHICH METASTASES WERE FOUND—FIVE CASES

Author	Operation	Result	Pancreatic Tumor Single or Multiple	Capsule	Blood Vessel Invasion	Insulin Extracted	Autopsy
1927 1 Wilder, Allan Power and Robertson ⁸³	Exploratory	Died postop	Multiple	Not described	Not described	Liver nodule	Metastases in liver, lymph node and mesentery
1934 2 Judd, Faust and Dixon ⁴⁴	Exploratory Tumor of pancreas and multiple metas- tases in liver. Bi- opsy of liver nodule	Died postop	Single	Original tumor not examined	Original tumor not examined	Not done	Not done
1935 3 Bickel, Mozer and Junet ⁹	None	Died without opera- tion	Single	Not described	Not described	Primary growth Liver nodule negative	Metastases in liver perito- neum and epi- cardium. Inter- stitial pancrea- titis
1937 4 Cragg, Power and Lindem ¹⁸	Exploratory Biopsy of liver nodule	Died postop	Diffuse through pancreas	None	Not described	Liver nodule	Metastases in liver and lymph nodes. Cyst of ovary
1938 5 Joachim and Banowitch ⁴¹	Resection of spleen and portion of tumor in tail of pancreas and a lymph node show- ing metastasis. Liver apparently negative	Died postop	Multiple	Not described	Not described	Not done	Not done

TUMORS OF ISLET CELLS

TABLE II

HYPOGLYCEMIA ISLET CELL TUMORS REMOVED AT OPERATION
CONSIDERED TO BE BENIGN—46 CASES

Author	Date	Single or Multiple	Capsule Micro- scopically	Blood Vessel Invasion	Insulin Extrac- tion	Result
1 Mathias ⁵¹	1928	Multiple	Islands in wall of cyst	Not described	0	Mild glycosuria postop
2 Carr Parker Grove Fisher and Larri- more ¹⁴	1931	Single	Complete	Not described	0	Symptom-free 7 yrs
3 Tomkies ⁶	1932	Single	Not described	Not described	0	Symptom-free 6 yrs
4 Derick Newton Schulz Bowie and Pokorny ¹⁷	1933	Single	Complete	Not described	+	Symptom-free 5 yrs
5 Graham and Womack ⁹	1933	2 tumors	Not complete	Not described	+	No attacks Permanent central nervous system damage 5 yrs
6 Ross ⁶⁷	1934	Single	Not complete	Not described	0	Symptom-free 2 yrs , 4 mos
7 Whipple and Frantz ⁵¹ (Case 1)	1935	Single	Complete	None	0	Symptom-free 68 mos
8 Whipple and Frantz ⁵¹ (Case 2)	1935	Single	Complete	None	0	Symptom-free 53 mos
9 Whipple and Frantz ⁵¹ (Case 3)	1935	2 tumors	Both incomplete	None	0	Symptom-free 25 mos- Died of duodenal hem- orrhage elsewhere 27 mos
10 Whipple and Frantz ⁵¹ (Case 4)	1935	2 tumors	Both complete	None	Unsuc- cessful	Symptom-free 57 mos
11 Whipple and Frantz ⁵¹ (Case 5)	1935	Single	Incomplete	None	0	Symptom-free 59 mos
12 Whipple and Frantz ⁵¹ (Case 6)	1935	Single	Incomplete	None	0	Symptom-free 56 mos
13 Wangenstein ⁷⁸ (Case 1)	1935	Single	Not described	Not described	0	Symptom-free 3 yrs 9 mos
14 Smith Hashinger and Engel ⁷⁹	1935	Single	Incomplete	Not described	0	Symptom free 30 mos
15 Jirasek Postranecky and Henner ³⁹ (Case 1)	1936	Single	Not described	Not described	0	Symptom-free 2 yrs
16 Gilmour ²⁸	1936	Single	Complete	Not described	0	Symptom-free 1 yr , 8 mos Then fainting spell after influenza Blood sugar 40 mg Well since
17 Harnapp ³¹	1936	Single	Incomplete	Not described	0	Symptom-free 2 yrs
18 Liu Loucks Chou and Chen ⁵⁰	1936	Single	Incomplete	Not described	0	Symptom-free 5 mos
19 Kepler and Walters ⁴⁶	1936	Single	Not described	Not described	0	Symptom-free 2 yrs 4 mos
20 McCaughan and Broun ⁵⁵ (Case 4)	1937	Single	Complete	Not described	0	Not relieved Re explored Resection impossible because of adhesions
21 Herman and Guis ³³	1937	Single	Complete	Tumor com- pletely calcified	0	Symptom free 2 yrs
22 Kusunoki and Munakata ⁴⁸	1937	Single	Complete	Not described	0	Symptom free 3 mos
23 Reiter ⁶⁵ (Case 2)	1937	Single	Complete	Not described	0	Symptom free 14 mos Has Gaucher s disease
24 Lukens and Ravdin ⁵⁹	1937	Single	Not described	Not described	0	Symptom-free 1 yr
25 Kalbfleisch ⁴⁵ (Case 2)	1937	Single	Complete	Not described	0	Relieved

TABLE II—Continued

26	Kalbfleisch ⁴⁵ (Case 3) Heupke and Obert ³⁶	1937	5 tumors	Complete	Not described	o	Died 2 days postop 4 of 5 tumors found at autopsy Adenoma of hypophysis and of para thyroid Hyperplasia of thymus
27	White and Gildea ⁸²	1937	Single	Complete	Not described	o	Symptom free 9 mos
28	Wangensteen ⁷⁸ (Case 3)	1937	Single	Not described	Not described	o	Symptom free 19 mos
29	Fraser MacLay and Mann ⁷⁵	1938	Single	Complete	Not described	o	Symptom free 5 mos
30	Jirásek and Postra necky ⁴⁰ (Case 2)	1938	Single	Not described	Not described	o	Symptom free 4 mos
31	Nicholson and Hart ⁸¹	1938	Single	Not described	Not described	o	Symptom free 18 mos
32	Parade and Kindler ⁸³	1938	Single	Complete	Not described	o	Complete recovery
33	Hermannsen and Nestmann ³⁵	1938	Single	Complete	Not described	o	Immediate relief of hypoglycemia Died postop Fever 41° C
34	Whipple ⁸⁰ (Case 9)	1938	2 tumors	1 Complete 2 Incomplete	None None	o	Symptom free 24 mos
35	Whipple ⁸⁰ (Case 11)	1938	Single	Incomplete	None	o	Symptom free 10 mos Question of pituitary tumor
36	Krauss ⁴⁷	1939	Single	Complete	Not described	o	Good recovery
37	Bergonzi ⁸	1939	Single	Not described	Not described	o	Died postop Autopsy No metastases Changes in cerebral cortex
38	Murphy Dustin and Bowman ⁵⁹	1939	Single	Incomplete	Not described	o	Relief of symptoms
39	West and Kahn ⁷⁹	1939	Single	Not described	Not described	o	Symptom free 14 mos
40	Akerberg ²	1939	Single	Not described	Not described	+	Died fourth day postop Pancreatitis and peritonitis 2 colloid adenomata in thyroid
41	Campbell Graham and Robinson ³ (Case 2)	1939	Single	Not described	Not described	+	Symptom free 20 mos
42	Campbell Graham and Robinson ¹³ (Case 3)	1939	Single	Not described	Not described	+	Symptom free 15 mos
43	Campbell Graham and Robinson ¹³ (Case 4)	1939	Single	Complete	Not described	+	Died third day postop Temp 107° F
44	Whipple (Case 13) (Not yet published)		Single	Incomplete	None	o	Symptom free 14 mos
45	Whipple (Case 14) (Not yet published)		Single	Incomplete	None	o	Died 56 hrs postop Temp 105.6° F Appearance that of thyroid crisis
46	Whipple (Case 16) (Not yet published)		Single	Incomplete	None	o	Symptom free 2 mos

first and fourth cases (Wilde¹, Allan, Power and Robertson⁸³ [1927], and Cragg, Power and Lindem¹⁶ [1937])

A review of published cases of tumors removed at operation, and considered benign (with our own series brought up to date), is given in Table II, with a brief abstract of certain features of the pathologic reports. It will be noticed that some cases listed by Whipple,⁸⁰ in 1938, are omitted, as these

TUMORS OF ISLET CELLS

TABLE III

HYPOGLYCEMIA ISLET CELL TUMORS FOUND AT AUTOPSY
CONSIDERED TO BE BENIGN—24 CASES

Author	Date	Single or Multiple	Capsule Micro- scopically	Blood Vessel Invasion	Insulin Ex- tracted	Autopsy
1 McClenahan and Norris ⁵⁶	1929	Single	Incomplete	Not described	o	No metastases
2 Smith and Seibel ³	1931	Single	Complete	Not described	o	No metastases Brain normal
3 Terbrüggen ⁷⁴ (Frank ⁷⁴ Case 1)	1931	Multiple	Complete	Not described	o	No metastases Atrophy of brain Chronic leptomenin- gitis Persistent thymus Two chief cell adenomata of hypophysis Liver low in glycogen
4 Buchner ¹¹ (Bielschowsky ¹⁰)	1932	Single	Complete	Not described	o	No metastases Patient a dia- betic originally Cirrhosis of pancreas
5 Barnard ⁴	1932	Single	Incomplete	Not described	o	No metastases Enlargement anterior lobe pituitary Brain normal
6 Cairns and Tanner ¹²	1933	Single	Complete	Not described	o	No metastases Brain normal
7 Gibbs ⁷⁷	1933	Single	Not described	Not described	o	No metastases Hemorrhagic cyst of adrenal
8 Wolf Hare and Riggs ⁸⁴	1933	3 tumors	Complete	Not described	o	No metastases Loss of cells in cortical layers of cerebrum
9 Reinhoff and Lewis ⁶⁶	1934	Single	Not described	Not described	Not suc- cessful	No metastases Enlarged thymus Adenomata of an- terior lobe of hypophysis Liver low in glycogen
10 Frank ⁷⁴ (Case 2)	1935	2 tumors	Not described	Not described	o	No metastases
11 Long Sheplin and Fishback ⁵¹	1936	Single	Not described	Not described	o	No metastases Carcinoma of sigmoid
12 Seino ⁷⁰	1937	Single	Complete	Not described	o	No metastases Atrophy of liver
13 Reiter ⁶⁵	1937	Single	Complete	Not described	o	No metastases
14 Kalbfleisch ⁴⁵ (Case 1)	1937	Single	Complete	Not described	o	No metastases
15 Ziskind Bayley and Mauer ⁸⁹	1937	Single	Incomplete	None	o	No metastases Thyroid normal
16 Jones and Matte ⁴²	1938	Single	Not described	Not described	o	No metastases Necroses in brain
17 Malamud and Grosh ⁵³	1938	Single	Complete	Not described	o	No metastases Diffuse de- generation of brain
18 Scheller and Stroebe ⁶⁹	1938	Single	Incomplete	Not described	o	No metastases
19 Levison and Ramsey ⁴⁹	1938	Single	Complete	None	o	No metastases Fatty de- generation of liver
20 Friedman ⁶ (Case 1)	1939	Single	Complete	Not described	o	No metastases Adenoma- tous hyperplasia of anterior lobe of pituitary Bilateral cortical adenomata of adrenal Adenomata of kidney ileum
21 Friedman ⁶ (Case 2)	1939	Single	Incomplete	Not described	o	No metastases Adenomat- ous hyperplasia of anterior lobe of pituitary and baso- philic infiltration of posterior lobe
22 Isaji ³⁸ (Case 1)	1939	Single	Complete	Not described	+	No metastases Hypophysis and adrenals slightly en- larged Cyst of parathyroid
23 Isaji ³⁸ (Case 2)	1939	Single with cyst- adenoma	Not described	Not described	o	No metastases Tuberculosis posterior lobe hypophysis
24 West and Kahn ⁷⁹ (Case 2)	1939	Single	Not described	Not described	o	No metastases

were personal communications to the author and no microscopic findings were available

It is interesting that in this series there is only one case with recurrence of symptoms (No 20), and one with a transitory episode following influenza (No 16). The case with persistent symptoms has been reexplored but further partial pancreatectomy was impossible because of adhesions. In cases with persistence or recurrence of symptoms, the presence of a second tumor must always be suspected, because of the numerous instances of multiple tumors, some removed simultaneously and others at successive operations.

A review of published cases of tumors found at autopsy and considered benign is given in Table III.

TABLE IV
HYPOGLYCEMIA ISLET CELL TUMORS REMOVED AT OPERATION
SUSPECTED OF BEING MALIGNANT—19 CASES

Author	Date	Single or Multiple	Capsule Micro- scopically	Blood Vessel Invasion	Insulin Ex- tracted	Result
1 Howland Campbell Maltby and Robin- son ³⁷	1929	Single	Incomplete	Not described	+	Symptom free 10 yrs
2 Womack Gnag and Graham E A. ⁸⁶	1931	Single	Incomplete	Not described	—	Symptom free 7 yrs
3 Bast Schmidt and Sevringhaus ⁵	1932	Single	Incomplete	Tumor in vessels	—	Symptom free 8 wks
4 Judd Allan Frank and Ryneerson ⁴³ (Case 6)	1933	Single	Not described	Not described	—	Symptom free 22 mos
5 Judd Allan Frank and Ryneerson ⁴³ (Case 7)	1933	2 tumors	Not described	Not described	—	Symptom free 23 mos
6 Graham E A and Womack. ⁹	1933	Single	Complete	Tumor in vessels	—	Symptom free 5 yrs
7 Wangenstein ⁷⁸ (Case 2)	1935	Single	Not described	Not described	—	Symptom free 39 mos Mental deterioration
8 Aitken ¹ (O Leary and Womack) ⁶²	1936	Single	Incomplete	Not described	—	Symptom free 2 yrs
9 Ryneerson ⁶⁸ (Case 1)	1936	Single	Not described	Not described	—	Died postoperative pneumonia No autopsy
10 Ryneerson ⁶⁸ (Case 2)	1936	Single	Not described	Not described	—	Died postoperative pneumonia No autopsy
11 Munakata ⁵⁸	1936	Single	Incomplete	None	—	Symptom free 4 mos
12 Ziskind and Bayley ⁸⁸	1937	2 tumors	Incomplete	Not described	—	Died 32 hrs postop Respiration failure Temp 107° F Au- topsy No metastases
13 Whipple ⁸⁰ (Case 8)	1938	Single	Incomplete	Tumor in vessels	—	Died of pneumonia 5 days postop No autopsy
14 Whipple ⁸⁰ (Case 10)	1938	Single	Incomplete	Tumor in vessels	—	Symptom free 17 mos
15 Forbes Davidson and Duncan ²³	1939	Single	Incomplete	Not described	—	Relieved of symptoms
16 Smith ⁷¹	1939	Multiple	Incomplete	Not described	—	Symptom free 5 mos
17 Beck and Segrest ⁶	1939	Single	Not described	Tumor in vessels	—	Symptom free 5 yrs 9 mos
18 Whipple (Case 12) (Not yet published)		Single	Incomplete	Tumor in vessels	—	Symptom free 13 mos
19 Whipple (Case 15) (Not yet published)		Single	Incomplete	Tumor in vessels	—	Symptom free 5 mos

TUMORS OF ISLET CELLS

A review of published cases of tumors removed at operation, and considered possibly malignant (with our own series brought up to date), is given in Table IV. In none of these, who survived operation, has there been any recurrence to date, and the long follow-up on some of these is noteworthy.

A review of the published cases of tumors found at autopsy, and considered possibly malignant, is given in Table V. It is noteworthy that in neither

TABLE V
HYPOGLYCEMIA ISLET CELL TUMORS FOUND AT AUTOPSY
SUSPECTED OF BEING MALIGNANT—THREE CASES

Author	Date	Single or Multiple	Capsule Micro- scopically	Blood Vessel Invasion	Insulin Extracted	Autopsy
1. Thalhimer and Murphy ⁷⁵	1928	Single	Incomplete	Not described	0	No metastases
2. Moersch and Kernohan ⁵⁷	1938	Single	Incomplete	Not described	0	No metastases Degenerative changes in brain

TABLE VI
SUMMARY OF THE STATISTICS IN TABLES I, II, III, IV AND V

Islet Cell Tumors with Hypoglycemia

	No. of Cases*
Tumors removed at operation and considered benign	46
Tumors found at autopsy and considered benign	24
Total benign tumors	70
Tumors removed at operation and suspected malignant	19
Tumors found at autopsy and suspected malignant	2
Total suspicious tumors	21
Carcinoma with metastases, proved malignancy	5
	—
Total islet cell tumors	96

* These statistics represent individual cases and do not include the number of multiple tumors found in some instances.

Pathology

Benign Cases *

Capsule	Complete	28	Blood vessel invasion	Stated absent	15
	Incomplete	20		Not described	55
	Not described	22			—
		—			70

* In these benign tumors there are reports of successful specific staining of the granules in the tumor cells 11 times. Insulin extractions of the tumors were done successfully eight times. These procedures were undertaken only on the operative material except for one insulin extraction.

Questionable Cases *

Capsule	Complete	1	Blood vessel invasion	Present	7
	Incomplete	15		Stated absent	1
	Not described	5		Not described	13
		—			—
		21			21

* In these questionable cases there are reports of successful specific staining of the granules in the tumor cells four times and successful insulin extraction once. All these were in operative material.

Proved Cases *

Capsule Probably not complete in any case—5 cases

Blood vessel invasion Not described—5 cases

* Sites of metastases: Liver, lymph nodes, mesentery, peritoneum and epicardium.

of these were metastases found. Also of interest in this table and Table III are the occurrence of changes in other endocrine glands, and the changes in the central nervous system, which confirm the clinical impression of the possibility of persistent mental deterioration in prolonged untreated cases.

It seems improbable that all of the tumors with histologic suggestion of carcinoma were really such, as the proportion of these to the benign tumors is so high, 21 to 70, and the follow-up in some cases is so long. It would be gratifying to feel that surgery had eliminated malignant disease in all these cases. But, of these suspected tumors, are there some in which blood vessel invasion, demonstrated, means that metastases, not demonstrable, were present at the time of removal of the primary growth, and will these eventually develop symptoms of hyperinsulinism?

If one wishes to consider the so-called "adenoma malignum" type of carcinoma of the thyroid as possibly analogous to these well-differentiated islet cell tumors with blood vessel invasion, then it might be that, like the thyroid tumors of this type, distant metastases might be late and slow. But the metastasizing tumors of the thyroid do not give evidence of their presence by hyperthyroidism, and it is conceivable that even in small metastatic foci of islet cell tumors hypoglycemia might occur early. Thus far no reported case has illustrated this, but it seems a good possibility. How long one should wait to feel secure about such functional metastases, and whether one can predicate that symptoms should appear early, is pure speculation. It will be of the utmost importance to follow all of these patients with these rare tumors for many years, and in the event of recurrence, or metastases after apparently successful removal, to publish such findings so that clinician and pathologist will have some basis for prognosis.

BIBLIOGRAPHY

- ¹ Aitken, L. F. Diagnosis and Treatment of Hyperinsulinism. *Med Clin North Amer*, 393, 413, 1936
- ² Akerberg, E. Hyperinsulinism and Surgery. *Acta chir Scandinav*, 83, 104-122, 1939
- ³ Bailey, O. T., and Cutler, E. C. Spontaneous Hyperinsulinism. Report of a Case with Localized Malformation of the Pancreas Simulating Tumor, and Treatment by Subtotal Pancreatectomy. *Jour Internat Chir*, 3, 1-26, 1938
- ⁴ Barnard, W. G. A Functioning Tumor of the Islands of Langerhans. *Jour Path and Bact*, 35, 929-932, 1932
- ⁵ Bast, T. H., Schmidt, E. R., and Sevringhaus, E. L. Pancreatic Tumor with Hypoglycemic Status Epilepticus. *Acta chir Scandinav*, 71, 82-192, 1932
- ⁶ Beck, J. E., and Segrest, G. O. Hyperinsulinism Cured by Removal of Islet Cell Adenoma. *J M A, Alabama*, 9, 40-43, 1939
- ⁷ Berardinelli, W. Hyperinsulinisme et hypoglycémie au cours d'un adenocarcinome du pancreas. *Presse med*, 422, 2098, 1934
- ⁸ Bergonzi, M. Basi anatomiche della ipoglicemia spontanea convulsivante e tumori a cellule insulari del pancreas. *Riv Sper di freniat*, 63, 161-195, 1939
- ⁹ Bickel, G., Mozer, J. J., and Junet, R. Diabète avec denutrition grave. Disparition de la glycosurie et atténuation progressive de l'hyperglycémie à la suite du développement d'un carcinoma insulaire du pancreas avec métastases hépatiques massives. *Bull et mem Soc med d hôp de Paris*, 51, 12-21, 1935

- ¹⁰ Bielschowsky, F Zur Klinik und Pathologie der Spontan-Hypoglykämie Klin Wchnschr, 11, 1492-1494, 1932
- ¹¹ Buchner, F Inselzellenadenom des Pankreas mit Hypoglykämie bei Diabetes Klin Wchnschr, 11, 1494-1496, 1932
- ¹² Cairns, R M, and Tanner, S E Adenoma of Islets of Langerhans Associated with Hypoglycemia Brit Med Jour, 1, 8-11, 1933
- ¹³ Campbell, W R, Graham, R R and Robinson, W L Islet Cell Tumors of the Pancreas Am Jour Med Sci, 198, 445-454, 1939
- ¹⁴ Carr, A D, Parker, R, Grove, E, Fisher, A O, and Latimore, J W Hyperinsulinism from B-Cell Adenoma of the Pancreas J A M A, 96, 1363-1367, 1931
- ¹⁵ Cottalorda, J, and Escarras Epithelioma langheransien Extirpation guérison Lyon chir, 30, 248-253, 1933
- ¹⁶ Cragg, R W, Power, M H, and Lindem, M C Carcinoma of the Islands of Langerhans with Hypoglycemia and Hyperinsulinism Arch Int Med, 60, 88-99, 1937
- ¹⁷ Derick, C L, Newton, F C, Schulz, R Z, Bowie, M A, and Pokorny, N A Hypoglycemia New Eng Jour Med, 208, 293, 1933
- ¹⁸ Dubois-Ferriere, H A propos d'un insulome de la queue du pancreas Existe-t-il des carcinomes par induction? Helvetica Med Acta, 6, 458, 1939
- ¹⁹ Evangelisti, T Sui carcinomi pancreatici a cellule di tipo insulare Policlinica (sez chir), 42, 384-402, 1935
- ²⁰ Fahri, A, and Sedad, A Contribution a l'etude des tumeurs malignes de la queue du pancreas Schweiz med Wchnschr, 10, 412-416, 1929
- ²¹ Fedoroff, P C Clinical Course of Hyperinsulinemia Vracp Gaz, 35, 586-592, 1931
- ²² Feinier, L, Soltz, S E, and Haun, P The Syndrome of Adenoma of the Pancreas Bull Neurol Inst, N Y, 4, 310-364, 1935
- ²³ Forbes, R D, Davidson, C F, and Duncan, J Hyperinsulinism Due to Tumor of the Pancreas Western Jour Surg, 47, 76-78, 1939
- ²⁴ Frank, H Letale Spontanhypoglykämie Munchen med Wchnschr, 82, 1829-1830, 1935
Idem Letale hypoglykämie bei Pankreasadenom Arch f klin Med, 171, 175-184, 1931
- ²⁵ Fraser, R, Maclay, W S, and Mann, S A Hyperinsulinism Due to a Pancreatic Islet Adenoma Quart Jour Med, 7, 115-135, 1938
- ²⁶ Friedman, N B Chronic Hypoglycemia Report of Two Cases with Islet Adenoma and Changes in Hypophysis Arch Path, 27, 994-1010, 1939
- ²⁷ Gibbs, C B F Insulin in Hypoglycemia New York State Jour Med, 33, 638, 1933
- ²⁸ Gilmour, C R, and Walton, C H A Hypoglycaemia Report of a Case Can M A J, 35, 547-549, 1936
- ²⁹ Graham, E A, and Womack, N A The Application of Surgery to the Hypoglycemic State Due to Islet Tumors of the Pancreas and Other Conditions Surg, Gynec and Obstet, 56, 728-742, 1933
- ³⁰ Hamdi, H Ein insulargenetisches Pankreasadenom (Insulom) Ztschr f Krebsforsch, 37, 411-413, 1932
- ³¹ Harnapp, G O Hyperinsulinismus Deutsch med Wchnschr, 62, 840-842, 1936, Monatschr f Kinderheilkunde, 65, 407-425, 1936, Acta Paediat, 22, 428-430, 1938
- ³² Henner, K, Jirasek, A, and Postranecky, O Hypoglycemia Due to Adenoma of Islands of Langerhans Čas lek česk, 75, 177, 1936
- ³³ Herman, S F, and Guis, J Relief of Hypoglycemic Symptoms by Removal of a Calcareous Pancreatic Tumor J A M A, 108, 1402-1405, 1937
- ³⁴ Herman, K Insulintumor und Hypoglykämie Munchen med Wchnschr, 82, 1361-1365, 1935
- ³⁵ Hermannsen, J, and Nestmann Hyperinsulinismus u Pankreasadenom Klin Wchnschr, 17, 1589, 1938

- ³⁶ Heupke, W , and Obert, L Die Spontanhypoglykamie u das hypoglykamische Syndrom
Munchen med Wchnschr , 84, 1937, 1937
- ³⁷ Howland, G, Campbell, W R, Maltby, E J, and Robinson, W L Dysinsulinism
Convulsions and Coma Due to Islet Cell Tumor of the Pancreas with Operation and
Cure J A M A , 93, 674-679, 1929
- ³⁸ Isaji, M On Islet Cell Adenoma and Islet Cell Carcinoma of the Pancreas Frankfurt
Ztschr f Path , 53, 178-207, 1939
- ³⁹ Jirasek, A J, Postranecky, O, and Henner, K Operation de l'hyperinsulinisme avec
hypoglycémie causée par un adenome des îlots de Langerhans, guérison Mem Acad
d Chir , 62, 584-592, 1936
- ⁴⁰ Jirasek, A, and Postranecky, O Un cas d'adenome des îlots de Langerhans Presse
med , 46, 671-672, 1938
- ⁴¹ Joachim, H, and Banowitch, M M A Case of Carcinoma of the Islands of Langerhans
with Hypoglycemia Ann Int Med , 11, 1754, 1938
- ⁴² Jones, W A, and Matte, M L Tumor of the Pancreas with Hypoglycemia Med
Bull Vet Admin , 14, 375, 1938
- ⁴³ Judd, E S, Allan, F N, Frank, N, and Ryneerson, E H Hyperinsulinism Its Surgi-
cal Treatment J A M A , 101, 99-192, 1933
- ⁴⁴ Judd, E S, Faust, L S, and Dixon, R K Carcinoma of the Islands of Langerhans
with Metastases to the Liver Producing Hyperinsulinism Report of Case Western
Jour Surg , 42, 555-557, 1934
- ⁴⁵ Kalbfleisch, H H Adenome inkretorischer Drüsen bei Hypoglykamie Frankfurt
Ztschr f Path , 50, 462-477, 1937
- ⁴⁶ Kepler, E J, and Walters, W Chronic Hypoglycemia Caused by Hyperinsulinism
Cure Effected by Removal of an Adenoma of the Pancreas Proc Mayo Clin , 11,
454-456, 1936
- ⁴⁷ Krauss, Hermann Zur Klinik und Therapie des Pankreasadenomes Deutsch Ztschr
f Chir , 251, 512-519, 1939
- ⁴⁸ Kusunoki and Munakata, M Noch ein weiterer Fall von Spontaner Hypoglykamie
Arch f klin Chir , 188, 272-278, 1937
- ⁴⁹ Levison, L A, and Ramsey, T L Spontaneous Hypoglycemia Associated with Pan-
creatic Adenoma Case Report with Operation and Autopsy Ohio State Med Jour ,
34, 869-872, 1938
- ⁵⁰ Liu, S H, Loucks, H H, Chou, S K, and Chen, K C Adenoma of Pancreatic Islet
Cells with Hypoglycemia and Hyperinsulinism Jour Clin Invest , 15, 249-260, 1936
- ⁵¹ Long, C F, Sheplin, L, and Fishback, D B Spontaneous Hyperinsulinism Due to
Pancreatic Adenoma in a Patient with Carcinoma of the Sigmoid A Catastrophic
Conjunction Am Jour Digest and Nutrit , 3, 488-489, 1936
- ⁵² Lukens, F W, and Ravdin, I S Adenoma of the Islet Cells of the Pancreas with
Operation and Recovery Am Jour Med Sci , 194, 92-96, 1937
- ⁵³ Malamud, N, and Grosh, L C, Jr Hyperinsulinism Due to an Islet Cell Adenoma of
the Pancreas with Destruction of the Cerebral Cortex A Preliminary Report Univ
Hosp Bull , Ann Arbor, Mich , 3, 70, 1937
Idem Hyperinsulinism and Cerebral Changes Report of a Case Due to an Islet Cell
Adenoma of the Pancreas Arch Int Med , 61, 579-599, 1938
- ⁵⁴ Mathias Adenomartige Inselwucherungen in der Wandung einer Pankreascyste Med
Klin , 24, 1814, 1928
- ⁵⁵ McCaughan, J M, and Broun, G O The Value of Partial Pancreatectomy in Con-
vulsive States Associated with Hypoglycemia ANNALS OF SURGERY, 105, 354-369,
1937
- ⁵⁶ McClenahan, W U, and Norris, G W Adenoma of the Islands of Langerhans with
Associated Hypoglycemia Am Jour Med Sci , 177, 93-97, 1929
- ⁵⁷ Moersch, F P, and Kernohan, J S Hypoglycemia Neurologic and Neuropathologic
Studies Arch Neurol and Psych , 39, 242-257, 1938

- ⁵⁸ Munakata, M Über einen Fall von Spontaner Hypoglykämie Arch f klin Chir , 185, 624-632, 1936
- ⁵⁹ Murphy, R G , Dustin, C C , and Bowman, R O Hyperinsulinism Due to Adenoma of the Pancreas Jour Lab and Clin Med , 24, 1050-1054, 1939
- ⁶⁰ Murray, Margaret R , and Bradley, C F Two Island Cell Adenomas of the Human Pancreas Cultivated *in Vitro* Amer Jour Cancer, 25, 98-107, 1935
- ⁶¹ Nicholson, Wm M , and Hart, D Spontaneous Hypoglycemia A Clinic (New) Internat Clinics, 2, 251-256, 1938
- ⁶² O'Leary, J L , and Womack, N Adenoma of Islands of Langerhans Histology Arch Path , 17, 291-310, 1934
- ⁶³ Parade, G W , and Kinder, K Inselzelladenom durch operation geheilt Klin Wchnschr , 17, 810, 1938
- ⁶⁴ Power, M H , Cragg, R W , and Lindem, M C Carcinoma of the Islands of Langerhans with Hypoglycemia Preparation of Insulin-like Extract from Metastatic Growth in the Liver Preliminary Report Proc Staff Meet, Mayo Clinic, 11, 97-101, 1936
- ⁶⁵ Reiter, G Über zwei Fälle von Inselzelladenom des Pankreas Klin Wchnschr . 16, 844-851, 1937
- ⁶⁶ Rienhoff, Wm F , Jr , and Lewis, D Surgical Affections of the Pancreas Met With in the Johns Hopkins Hospital from 1889 to 1932, Including a Report of a Case of an Adenoma of the Islands of Langerhans and a Case of Pancreatolithiasis Bull Johns Hopkins Hosp , 54, 386-429, 1934
- ⁶⁷ Ross, Lloyd I , and Tomasch, John M Hyperinsulinemia Secondary to an Adenoma of the Pancreas Report of a Case Arch Surg , 28, 223-231, 1934
- ⁶⁸ Ryneerson, E H Adenoma of the Islands of Langerhans Report of Two Cases Proc Mayo Clinic, 11, 451-454, 1936
- ⁶⁹ Scheller, H , and Stroebe, F Hypoglykämische Anfälle bei Inseladenom mit Ausgang in hyperglykämisches Coma Monatschr f Psychiat u Neurol , 99, 520-531, 1938
- ⁷⁰ Seino, Yutaka Zur Klinik der Spontanhypoglykämie, Ztschr f klin Med , 131, 770-780, 1937
- ⁷¹ Smith, Joseph Hyperinsulinism Wisconsin Med Jour , 38, 283-286, 1939
- ⁷² Smith, L B , Hashinger, Edw H , and Engel, L P Hyperinsulinism Due to Adenoma of Islets of Langerhans Jour Kansas Med Soc , 36, 363-367, 1935
- ⁷³ Smith, M G , and Seibel, M G Tumors of the Islands of Langerhans and Hypoglycemia Am Jour Path , 7, 723-739, 1931
- ⁷⁴ Terbruggen, August Anatomische Befunde bei spontaner Hypoglykämie infolge multipler Pankreasinseladenome Beitr z path Anat u z allg Path , 88, 37-50, 1931
- ⁷⁵ Thalhimer, W , and Murphy, F D Carcinoma of the Islands of the Pancreas Hyperinsulinism and Hypoglycemia J A M A , 91, 89-91, 1928
- ⁷⁶ Tomkies, J S Adenoma of Islet Cells of Pancreas with Hyperinsulinism and Hypoglycemia Operation and Recovery Texas State Jour Med , 28, 523, 1932
- ⁷⁷ Vecchi, A Adenoma maligno delle isole di Langerhans in un pancreas aberrante Arch per le sc med , 38, 277-309, 1914
- ⁷⁸ Wangensteen, O H The Surgery of Hyperinsulinism Minn Med , 18, 265-267, 1935
Idem Surgical Diseases of the Pancreas Minn Med , 20, 566, 1937
- ⁷⁹ West, W F , and Kahn, M Adenoma of Pancreas with Hyperinsulinism Two Proved Cases in Cousins with Surgical Cure in One West Jour Surg , Obst and Gynec , 47, 364, 1939
- ⁸⁰ Whipple, Allen O The Surgical Therapy of Hyperinsulinism Jour Internat Chir , 111, 1-35, 1938
- ⁸¹ Whipple, Allen O , and Frantz, V Kneeland Adenoma of Islet Cells with Hyperinsulinism ANNALS OF SURGERY, 101, 1299, 1935

- ⁸² White, B V, Jr, and Gildea, E F Adenoma of the Pancreas and Hyperinsulinism
New Eng Jour Med, 217, 307-313, 1937
- ⁸³ Wilder, R M, Allan, F N, Power, M H, and Robertson, H E Carcinoma of the
Islands of the Pancreas Hyperinsulinism and Hypoglycemia J A M A, 89, 348-
355, 1927
- ⁸⁴ Wolf, A, Hare, C C, and Riggs, H W Adenoma of Pancreas Bull Neurol Inst,
3, 232, 1933
- ⁸⁵ Womack, N A Hypoglycemia Surgery, 2, 793-811, 1937
- ⁸⁶ Womack, N A, Gnagi, W B, and Graham, Evarts, A Adenoma of the Islands of
Langerhans with Hypoglycemia J A M A, 97, 831, 1931
- ⁸⁷ Zanetti, G Contributo allo studio dei tumori del pancreas Arch per le sc med,
49, 505-519, 1927
- ⁸⁸ Ziskind, E, and Bayley, W A Hyperinsulinism Jour Lab and Clin Med, 23,
231-240, 1937
- ⁸⁹ Ziskind, E, Bayley, W, and Mauer, E F Hyperinsulinism Arch Int Med, 60,
753-771, 1937

ACUTE PANCREATITIS AND DIABETES

HARRIS B SHUMACKER, JR, M D

BALTIMORE, MD

FROM THE DEPARTMENT OF SURGERY, YALE UNIVERSITY SCHOOL OF MEDICINE, AND THE SURGICAL CLINIC, NEW HAVEN HOSPITAL, NEW HAVEN, CONN

DURING the past year I have had the opportunity to thoroughly study a patient, known to have been free of diabetes previously, who developed severe persistent diabetes mellitus during convalescence from acute hemorrhagic pancreatitis. A cursory survey of the literature revealed a wide diversity of opinion concerning the rôle of acute pancreatitis in the production of diabetes. On the one hand, the incidence of diabetes as a sequela was not only obviously rare, but most authors writing on acute pancreatitis had neglected to note it as a possibility or had merely mentioned it in passing. On the other hand, certain investigators interested in metabolic diseases have expressed the view that even mild, unrecognized attacks of pancreatitis may be an important factor in causing diabetes or in bringing about exacerbations of preexisting diabetes. This divergence of thought has made it advisable to restudy the problem. I shall first report in some detail my own case, secondly, summarize the pertinent data from a series of cases of severe pancreatitis from the New Haven Hospital, and finally, review the literature.

Case Report—T M, male, age 27, was admitted to the New Haven Hospital, February 17, 1938, complaining of severe epigastric pain. There had been no diabetes in the family. The past history was irrelevant except for occasional bouts of drinking. There was nothing suggesting diabetes, no polyphagia, polydipsia, polyuria, or weight loss. He had been previously admitted, late in 1934, with a gonococcal urethritis, prostatitis, and arthritis. Five weeks before admission he had been confined to another hospital in the city with a brief attack of right lower quadrant pain. His urine had never shown sugar. In general he had been quite well. For a week he had had anorexia and occasional mild epigastric postprandial discomfort. Three days before admission he had a stool which he described as "black."

The present illness began at 8 A M on the morning of February 17, when he was suddenly seized with excruciating epigastric pain which "bore through" to his back and which persisted. He began to vomit almost immediately and continued to vomit frequently. There was no gross blood in the vomitus. At noon and again at 10 30 P M his physician gave him a hypodermic of morphine. Finally, at midnight he was sent to the hospital.

Physical Examination—Temperature 100.6° F, pulse 86, respirations 24, blood pressure 120/76. He appeared to be in agonizing pain and was obviously very ill, sweating profusely, vomiting frequently. The abdomen moved little with respiration, was board-like in the epigastrium, less spastic in the lower quadrants, and extremely tender all over, but especially in the midepigastrium. There was generalized rebound tenderness. There was no distention, no shifting dullness. There was no obliteration of liver dullness. The examination was otherwise not remarkable. The blood examination showed Erythrocytes 5,400,000, hemoglobin 100 per cent, leukocytes 16,000, 96 per cent neutrophils and 32 per cent nonsegmented forms. The urine examination. Specific gravity

Submitted for publication April 13, 1939

1034, acid, albumin 2 plus, sugar negative, acetone 2 plus, rare white cells It was the impression that the patient had a perforated peptic ulcer

On the way to the operating room roentgenograms were taken which were negative for pneumoperitoneum A Wangenstein stomach suction was instituted While waiting, at the patient's request, for a priest to arrive, the pulse began to rise and blood pressure to fall, and in spite of an infusion of glucose and saline his pulse had risen to 160 and his systolic pressure had dropped to 60 by the time the operation was begun

Operation—Under ether and venethene anesthesia supplemented with local infiltration, the peritoneal cavity was entered through a small upper right rectus incision and a large amount of "tomato soup" fluid was immediately encountered There were extensive and marked fat necroses There was a mass in the region of the pancreas, some omental adhesions over the duodenum, and no evidence of ulcer Through the foramen of Winslow was emitted much dark blood-stained fluid The lesser sac was entered through the gastrocolic ligament The pancreas was about twice the normal size, the head being somewhat more enlarged than the body and tail The entire organ was soft, necrotic, and discolored with ecchymoses Two Penrose drains were inserted, one toward the head of the pancreas, the other toward the tail The gallbladder and the common duct appeared and felt normal A cholecystostomy was performed and the wound closed By the end of the procedure the patient had received 1,900 cc of glucose and saline solution and the blood pressure had risen to 100/50 A transfusion of 500 cc of citrated blood was given The blood pressure was now 125/68 and the pulse 110

The patient did well His temperature rose on the first day to 102.8° F, but fell promptly, and ranged between 99° and 100.5° F for the next five days, after which it was normal For a few days he was somewhat delirious The wound drained profusely for 24 hours, but little thereafter The drain was removed on the eighth day A lipiodol visualization of the biliary tract on March 1, 1938, showed normal gallbladder and cystic and common ducts The following day the catheter was removed, and two days later the wound was closed and an intravenous cholecystogram was made This showed nonvisualization, which was interpreted as a postoperative effect A liver function test (tetra-iodo-phenolphthalein) revealed 5 per cent retention in 30 minutes

The admission urine had been negative for sugar After operation and infusion there was complete reduction of Benedict's solution and only a trace of acetone Glycosuria persisted When he was put on a measured diet (P 70, F 150, C 150) on February 25 most of the fractional specimens were showing complete reduction He improved somewhat, and when he was finally discharged, March 6, 1938, he was only occasionally excreting sugar on a diet of P 80, F 175, C 200 The blood sugar had been 111 mg per cent on February 22 It was 104 on February 26, and a glucose tolerance test revealed a fall to only 157 in two hours This was repeated on March 1 The fasting value was 124, it rose to 214 in one hour, and was 191 in two hours

On return to the clinic, March 9, 1938, he was weak and thirsty and had polyuria and mild abdominal discomfort The urine showed complete reduction of Benedict's solution, but no acetone

He was readmitted, May 30, 1938, complaining of excessive hunger, thirst, and polyuria He had not adhered to his diet He said that he had been drinking six to eight quarts of milk, three to four quarts of water, and ten bottles of beer a day He had been to the clinic only once, to his family doctor once, and had tested his urine himself only three times On all occasions, it showed complete reduction He had had marked polyuria, cramps in his calves the past few nights, and some constipation He had had mild epigastric pain about twice a week for which, in spite of advice to the contrary, he had taken beer He had lost about 20 pounds He was definitely acidotic Fractional specimens of urine showed complete reduction of sugar and from

2 to 4 plus acetone. He was immediately started on insulin therapy and after 48 hours the acetone disappeared from the urine for the most part. Insulin was rapidly increased from 30 units a day to a maximum of 110 units on June 8, when for the first time he became relatively free of glycosuria. He was now on a diet of P 100, F 250, C 300, and was constantly complaining of hunger. He was discharged, June 14, on this diet, with 55 units before breakfast and 30 units before supper, on which regimen he was moderately well regulated. On May 31 the blood sugar was 158 and cholesterol 450. On June 8 the blood sugar was 219. A bromsulphalein liver function test showed no retention in 40 minutes, intravenous cholecystograms showed poor filling but prompt emptying after a fatty meal, probably due to his recent cholecystostomy. He had gained ten pounds and now weighed 152.

He was readmitted, August 27, 1938, with an attack of abdominal pain similar to but less severe than his original one, and it was felt that he might be suffering from a mild recurrence of pancreatitis. This attack cleared up under conservative therapy. He had not followed his diet or taken his insulin for a month and had indulged in bouts of drinking. His diabetes was finally regulated on a diet of P 90, F 200, C 200 with 30 units before breakfast and 15 units before supper. Liver function test again showed no retention of dye. Blood sugar was 182 mg per cent on September 6. On discharge, September 13, he weighed 156 pounds.

On November 17, 1938, he was again sent into the hospital for regulation. He had taken his insulin (except occasionally when drunk), his urine had recently showed a "brick-red" test, he was constantly hungry and thirsty, and he was drinking about nine quarts of milk a day and soda pop "incessantly." He had polyuria, weakness, and fatigability. For two weeks he had had a "cold in the chest" and was producing about a cup of foul sputum a day. He had a diffuse rash. Kahn and Wassermann reactions were positive. The urine showed complete reduction of Benedict's solution and much acetone. A diagnosis of secondary syphilis and pyogenic right upper lobe abscess was established. The former was treated with bismuth and mepharsen, the latter by postural and bronchoscopic drainage. The abscess resolved. He was discharged, December 30, 1938, on a diet of P 90, F 250, C 175 with 30 units of insulin before breakfast and 15 units before supper.

Three days later he was seen again with a respiratory infection. At this time he had marked glycosuria, and his insulin was increased to 30-0-30. The following day there was again glycosuria and acetonuria, and hospitalization was advised. He went to another hospital where he remained for three weeks. Since then he has continued with antileptic therapy. His diabetes remains exceedingly difficult to regulate.

NEW HAVEN HOSPITAL SERIES

The case just presented is the only instance in the New Haven Hospital in which diabetes has developed as a complication or sequela of acute pancreatitis. During the past 17 years there have been 18 cases of severe acute hemorrhagic pancreatitis. The pertinent data are recorded in Table I. Mild cases of pancreatitis and suspected cases not proved by operation or autopsy are excluded. The patients varied in age from 24 to 68 years, six were males, 12 females. All except one were subjected to operation. Six of 17 patients treated by operation died, a mortality of 35 per cent. Case 7 was known to have diabetes. Excluding this case, four, or 27 per cent, showed glycosuria.

* Since submission of this paper for publication the diabetes of the patient, T M, has remained severe. He was admitted in a diabetic coma in September, 1939. He now requires about 75 units of insulin daily. Following the lung abscess he developed bronchiectasis in the right upper lobe, and in November, 1939, he was found to have contralateral apical tuberculosis with cavitation. He is now under treatment for this in a Sanitarium.

at some time during the acute illness, though only one (6 per cent) had glycosuria on admission. Two of the four patients with glycosuria died. Three patients upon whom blood sugar determinations were made showed some elevation.* Only one patient developed diabetes. Careful follow-up studies are not available, although several patients seen at varying intervals after operation were in apparent good health. A few of the cases are of some particular interest.

TABLE I

CASES OF SEVERE ACUTE HEMORRHAGIC PANCREATITIS IN THE NEW HAVEN HOSPITAL

No	Year	Name	Age	Sex	Diagnosis Established By		Glycosuria		Blood Sugar	Outcome	Remarks
					Opera- tion	Autopsy	On Admission	Subse- quently			
1	1921	M W	48	F	Yes	No	No	No		Died	Urine negative 5 mos later
2	1923	A H	59	F	Yes	No	No	No		Recovered	
3	1923	N H	47	F	Yes	No	No	No		Recovered	
4	1923	E H	52	F	Yes	No	No	No		Recovered	
5	1924	J B	56	M	Yes	No	No	No		Recovered	
6	1925	J M	62	M	Yes	No	No	No		Recovered	
7	1926	H K	68	F	No	Yes	Yes	Yes	469	Died	Known diabetic for 5 yrs (see text)
8	1928	I E	29	F	Yes	No	No	No		Recovered	
9	1930	E G	32	M	Yes	No	No	No		Recovered	Questionable recurrence 3½ yrs later. Urine negative
10	1931	P H	36	F	Yes	No	No	No		Recovered	
11	1932	O S	63	M	Yes	No	No	No		Died	
12	1932	M B	31	F	Yes	No	No	No		Recovered	
13	1934	C C	48	F	Yes	No	No	Yes	155	Died	See text
14	1936	E R	45	F	Yes	No	Yes			Died	
15	1936	H S	45	F	Yes	Yes	No	No		Died	
16	1936	G H	30	M	Yes	Yes	No	No		Died	
17	1938	T M	27	M	Yes	No	No	Yes	124	Recovered	Diabetes developed (see text)
18	1938	M D	24	F	Yes	No	No	Yes	150	Recovered	Urine negative 8 mos later (see text)

ILLUSTRATIVE CASE REPORTS

Case 7—This 68-year-old female was admitted in coma. A diagnosis of mild diabetes had been established five years previously. No glycosuria had been observed when she was seen at intervals after that time. Five days before admission she caught cold and glycosuria appeared. It increased as the upper respiratory infection became worse, but three days before admission she was practically well. Frequency and polydipsia began and she became stuporous 24 hours before admission. She was brought to the hospital in coma. There was upper abdominal tenderness and the diagnosis of acute pancreatitis was considered. In spite of intensive therapy, the coma persisted and she died within a few hours. At autopsy acute hemorrhagic pancreatitis and cholelithiasis with calculi in the common duct and in the duct of Wirsung were found.

This case is instructive from two points of view. First, as an example of how disastrous acute pancreatitis may be in a patient with relatively mild diabetes, and secondly, how hazardous it is to attribute diabetic coma in

* Normal values in the New Haven Hospital range from 55 to 75 mg per cent

acute pancreatitis to the latter process alone unless the patient is known not to have been a diabetic previously

Case 13—This 48-year-old woman was admitted with acute pancreatitis of nine hours' duration. She had had a previous admission for acute cholelithiasis, at which time the urine was sugar free. The urine on this admission contained albumin and acetone, but no sugar. A postoperative sample of blood showed a sugar of 155 and N P N of 42. The next morning, several hours after an infusion of glucose and saline, the blood sugar was 251, the N P N 47. The patient had received some morphine. She failed to respond. The first impression was that she was in a diabetic coma. There was an acetone breath. The blood pressure was 92/50. She was given blood, glucose and saline intravenously, and insulin. An hour and a half later she responded. The urine during this period showed complete reduction and 1 plus acetone. Four hours after the last dose of insulin the blood sugar was 76. The next day it was 62 and she was given no insulin. She had signs of pneumonia. She was given a little insulin off and on, but had no further glycosuria. She developed a pneumococcus septicemia and died after seven days in spite of repeated transfusions and other supportive measures.

This patient undoubtedly had some disturbance of carbohydrate metabolism, though it is, at least, to be questioned whether her period of coma was really due to hyperglycemia and acidosis.

Case 18—This patient was a 24-year-old woman who had had several attacks suggesting acute cholecystitis. She was admitted in an attack differing from the others in that there was a great deal of left upper quadrant as well as right upper quadrant pain. There were signs of diffuse peritoneal irritation. At celiotomy, acute hemorrhagic pancreatitis and chronic cholecystitis with cholelithiasis were found. The lesser sac was drained and a cholecystostomy performed. During convalescence she sloughed considerable quantities of pancreatic tissue. There was no glycosuria on admission, but complete reduction following operation and again the next day after an infusion of glucose. The following day the sugar was 1 plus, and on several occasions during the week there was a trace of sugar in the urine. There were never acetone bodies. The blood sugar was slightly elevated on several occasions, 107 to 150 mg per cent. A glucose tolerance test on the twenty-fourth postoperative day revealed values of 150, 282, 216, 112 and 104 (fasting, one-fourth, one-half, one and one-half and two hours) and on the fortieth postoperative day values of 98, 199, 125, 99 and 93 mg per cent (fasting, one-fourth, one-half, one and two hours). Her family doctor writes that her health has remained good and that her urine was normal when last examined, nine months after operation. This patient had a mild transient interference with carbohydrate metabolism.

Although my concern has been primarily with the association of true diabetes mellitus and acute pancreatitis and not with those transient manifestations of disturbed carbohydrate metabolism which are occasionally observed during the course of acute pancreatitis, it will be advisable to consider the latter briefly since they may shed some light upon the former.

Glycosuria—In Reginald Fitz's original communications^{1, 2} on acute pancreatitis the occurrence of glycosuria is not mentioned. In 1895, Atkinson³ reported a fatal case of gangrenous pancreatitis with slight glycosuria. Thirty years earlier, Harley⁴ had reported a case of long-standing obstruction of the pancreatic and common bile ducts with pancreatic abscess in which there was terminal glycosuria. Six of the 44 instances of acute pancreatitis described by Korte⁵ were associated with glycosuria. Most authors since then have noted this in approximately the same percentage of cases—Egdahl⁶ in 5 per

cent, Guleke⁷ in 10 per cent, Sebening⁸ in 10 per cent, Beinhard⁹ in 12 per cent, and Mahnei¹⁰ in 10 per cent. All are agreed that glycosuria is found in such a small proportion of patients, and is not always found, even then, on the first examination, as to make it of little help in the differential diagnosis.

In 1927, Schmieden and Sebening^{11, 12} presented a study of 1,278 operatively treated cases of acute pancreatitis collected from the literature and from personal communications in the postwar period. To these I have added, in Table II, an additional 1,600 cases, gathered from the literature, since the time of their report.^{*} Data are available on about 700 of these in which glycosuria occurred about 78 times, or approximately 11 per cent.

Hyperglycemia—In 1924, Calzavara⁸⁷ reported that, in experimentally induced acute pancreatitis in dogs, hyperglycemia was an early and constant finding, reaching a maximum in six hours (often ten times the normal value) and persisting to death. If the pancreas was drained the blood sugar gradually fell. There was no glycosuria. He ventured to suggest that this observation might be found clinically and be of considerable diagnostic importance. Douglas,⁷¹ among others, states that blood sugar determinations have not proved to be of any great value in the early diagnosis of acute pancreatitis, and Fiessinger⁸⁸ says that hyperglycemia is as inconstant as is glycosuria. Others,^{25, 51, 89 to 96} however, claim that hyperglycemia occurs very frequently and is of considerable diagnostic aid. Although he had only a few determinations, Biocq⁹⁷ suggested, in 1926, that if hyperglycemia should be found with any regularity it might prove of great importance for diagnosis and prognosis. Later, he and Varangot⁸¹ collected from the literature 72 cases in which blood sugar determinations were available, and of these 15 had values of less than 150, 23 from 150 to 200, and 34 over 200 mg per cent. Gabrielle⁹² states that hyperglycemia is a constant finding, and Bernhard⁸⁹ points out that the blood sugar may be normal in mild cases though it is elevated in most severe cases of acute pancreatic necrosis. Wildegans^{93, 94} agrees with the latter opinion, but states that there is hyperglycemia in all severe cases and that this determination is of prime diagnostic value. Because other acute abdominal diseases may occasionally be associated with a mild hyperglycemia, it has been suggested^{81, 84} that only values of 200 mg per cent or more be considered of diagnostic importance. Perhaps, because of the varying normal values with different technics, it should be considered of significance if the blood sugar is elevated to about twice the normal level.

In Table II data are available in 55 cases. Of these, 28 patients, or 50 per cent, had blood sugars of 200 or more, nine (18 per cent) between 150 and 200, and six additional cases showed slight elevation (125 to 150 mg per cent). In addition, Keischnei²³ states that there were four patients with hyperglycemia in a series of 41 cases without stating the number upon whom determinations were made. The question arises whether the relatively high

* An attempt has been made to limit the selection of cases to those of relatively severe acute pancreatitis, proved by operation or autopsy, and this has been done except in a few instances where reports have included a small number of cases not so proven.

TABLE II

CHANGES IN CARBOHYDRATE METABOLISM IN AND FOLLOWING ACUTE PANCREATITIS

Author	No of Cases	No Surviving	No With Glycosuria	No With Hyperglycemia	No Followed by Disturbed Glucose Tolerance But Not True Diabetes	No Followed by Diabetes	Remarks
Schmieden and Sebening ¹¹ (1927)	1,278	624				18	
Brutt ¹³ (1927)	33	20			*	1†	* Most cases studied soon after acute illness † See Table V
Von Redwitz ¹⁴ (1927)	1	1		0		1*	* See Table V
Kummer ¹⁵ (1927)	8	3	2				
Warfield ¹⁶ (1927)	2	0	2	1		2*	* See Table V
Watkins ¹⁷ (1928)	18	8	2	1*			* Another had blood sugar of 150 mg %
Delmore ¹⁸ (1928)	13	11					
Kreiner ¹⁹ (1928)	2	1	1	1*		0	* Another had blood sugar 21% above normal
Grant ²⁰ (1928)	12	5	2				
Ney ²¹ (1929)	28	28	3	1	3	5*	13 of the 28 were examined in follow-up studies * See Tables IV and V
Walzel ²² (1929)	40	20		1		2*	* Cleared up after drainage of pseudocysts
Kerschner ²³ (1929)	41	12	Few	4		2*	* See Table III
Tammann ²⁴ (1929)	38	18			6*	0	* 12 cases studied
Jorns ²⁵ (1929)	18	18	Few	6	5*	1†	* 7 cases studied † See Table V
Linder and Morse ²⁶ (1929)	88	65					
Olds ²⁷ (1929)	7	5	0	1			
Simon ²⁸ (1929)	6	1					
Kramer ²⁹ (1920)	7	4	0				
Cullen and Friedenwald ³⁰ (1929)	4	1	2*			*	* One case of preexisting diabetes
Oehler ³¹ (1929)	26	11	0				
Warren ³² (1930)	6	0				6*	* See Table III
Eliason and North ³³ (1930)	14	7	1				
Bayer ³⁴ (1930)	1	0	1	1		1*	Died in coma * See Table III
Weeden ³⁵ (1930)	12	4					
Stocker ³⁶ (1930)	36	15					
Matthaes ³⁷ (1931)	21	21			2	1*	* See Table III
Bernhard ³⁸ (1931)	75	50	9		5*	5†	* 25 cases studied † See Tables III and V
Hopkins ³⁹ (1931)	1	1	0			0	
Dunn ⁴⁰ (1931)	1	0	1			0	
Mackechne and Olsen ⁴¹ (1931)	1	1	0	0	*	0	* Blood sugar 134 about a month after operation
Grant ⁴² (1931)	4	1		2			
Unger and Sostmann ⁴³ (1931)	100	54			5*	1†	* 16 cases studied † Another case of preexisting diabetes See Table V
Kappis ⁴⁴ (1931)	75	38					
Martens ⁴⁵ (1931)	122	68	12			1*	* See Table V
Rich ⁴⁶ (1932)	6	4	1	0			
Felsenreich ⁴⁷ (1932)	32	11	4			1*	* Another known diabetic died in coma See Table IV
McWhorter ⁴⁸ (1932)	64	29	8*			1†	* 5 of these died † See Table V
deTakats and MacKenzie ⁴⁹ (1932)	30	19	4	*	2†	2†	* 2 showed mild hyperglycemia one an altered glucose tolerance curve on fifth post day † 4 studied † See Table V
Jones ⁵⁰ (1932)	1	1		*		0	* Blood sugar was 140 mg %

TABLE II (Continued)

Author	No of Cases	No Surviving	No With Glycosuria	No With Hyperglycemia	No Followed by Disturbed Glucose Tolerance But Not True Diabetes	No Followed by Diabetes	Remarks
Lyall ⁸¹ (1932)	3	0					
Quick ⁸² (1932)	49	22	3		2	1	11 cases studied See Table V
Downie ⁸³ (1932)							
Lemieux ⁸⁴ (1932)	1	1				1*	* See Table V
Truesdale ⁸⁵ (1932)	54	43				*	* One patient died in coma presumably a preexisting diabetic
Haynes ⁸⁶ (1933)	6	5					
Hartlieb ⁸⁷ (1933)	27	13					
Jacobovici ⁸⁸ (1933)	14	8	2*	1		*	* A patient with preexisting diabetes
Thomas ⁸⁹ (1933)	3	2	0				
Finney ⁹⁰ (1933)	32	20					This includes the cases reported by Rienhoff and Lewis ⁶¹
Koster and Kasman ⁶ (1934)	22	17	2				
Horne ⁶³ (1934)	13	7	1	0			
Harve ⁶⁴ (1935)	11	9			1		
Donald ⁶⁵ (1935)	6	4	1				
LeSage and LeSage ⁶⁶ (1935)	4	4	0				
Henderson and King ⁶⁷ (1935)	60	28	4				
Dobbs ⁶⁸ (1935)	15	6	1				All cases of acute pancreatitis in children
Huet ⁶⁹ (1935)	1	1					
Douglas ⁷⁰ (1933)	38	20				*	* One patient died in coma presumably an old diabetic
Douglas ⁷¹ (1935)							
Mendelssohn ⁷ (1936)	6	3	0				
deKlimko ⁷² (1936)	19	8			3*	0	* 6 cases studied
Rochet ⁷⁴ (1936)	6	3					
Mahner ¹⁰ (1937)	19	13	3				
Joslin ⁷⁵ (1937)	1	1	0			1*	* See Table V
Jurist ⁸ (1909)							
Weir ⁷⁷ (1937)	47		3				
Gatewood ⁷⁸ (1937)	2	2	0				
Sedgley ⁷⁹ (1937)	2	2	0			0	
Trasoff and Scarf ⁸⁰ (1937)	16	4		10*			* All 10 cases studied had values of 190 mg %—or more
Brocq and Varangot ⁸¹ (1937)	1	1	1	1		1	A case of temporary diabetes
Kufferath and Volkmann ⁸ (1938)	65	44					
Beck ⁸³ (1938)	10	2	1	3		*	* One patient with a history of glycosuria for 10 mos died in coma
Dunlop and Hunt ⁸⁴ (1938)	11	7	2	6*			* Only 6 cases studied
Hunt ⁸⁵ (1928)							
Abell ⁸⁶ (1938)	30	21					

percentage of patients with elevation of blood sugar is due to omission from published reports of normal values. It may be said, however, that individual reports are in agreement. For example, Joins²⁵ found hyperglycemia in all of eight patients studied (three over 200, four over 150 mg per cent), Trasoff and Scarf⁸⁰ in all of ten patients studied (all over 190 mg per cent), and Dunlop and Hunt⁸⁴ in all of six patients studied (five over 200 mg per cent).

Bernhard⁸⁹⁻⁹⁸ feels that a glucose tolerance test is of greater diagnostic aid than is fasting blood sugar estimation. He states that mild cases of acute pancreatitis in which there may be no hyperglycemia are likely to show an abnormal glucose tolerance curve. Furthermore, he states that, though

other acute abdominal conditions, *e g*, empyema of the gallbladder, may occasionally manifest hyperglycemia, they do not show the changes in glucose tolerance which he considers characteristic of acute pancreatitis. There are few instances in the literature in which this test has been recorded, but where it has been used it has apparently borne out his observation. Mikkelsen⁹⁹ agrees that this is a more helpful procedure in diagnosis than blood sugar determination, and Wildegans,⁹⁴ likewise, feels that in mild cases of pancreatitis it is of greater assistance. Tioissier, Baiety, and Gabriel¹⁰⁰ have recorded an unusual case with a reversed hyperglycemia glucose tolerance curve.

A number of authors^{9, 66, 101} have suggested that the occurrence of marked glycosuria, or more especially of hyperglycemia, may be a bad prognostic sign. Certainly, many examples may be cited in support of this opinion in addition to the fatal cases of true diabetes which will be discussed subsequently. Neumann¹⁰² had a patient who was admitted on the second day of his illness with 6.5 per cent sugar in the urine and acetone breath, who died the day after operation. Dunn⁴⁰ lost a patient whose urine was loaded with sugar within 29 hours of the onset of symptoms. Bernhard⁹ had a fatal case in which the blood sugar rose in 18 hours from 260 to 370 mg per cent. Dunlop and Hunt,⁸⁴ likewise, reported a case in which the blood sugar rose from 210 on the first postoperative day to 360 mg per cent before death, on the fifth day. One of Grant's⁴² fatal cases had a blood sugar of 400 mg per cent. Geinitz¹⁰³ lost a patient who had glycosuria and a blood sugar of 341 mg per cent in spite of the use of insulin. Walzel²² had a patient with a sugar of 340 mg per cent 12 hours after operation who died in 36 hours in spite of insulin therapy. Whipple and Speese¹⁰¹ describe the case of a patient whose blood sugar was 384 mg per cent the day after operation. Insulin failed to control the blood sugar after two weeks, and the patient died within four weeks. There was only slight glycosuria on a few occasions and never acetonuria. On the other hand, many instances might be presented in which there has been marked hyperglycemia and recovery. Of the 28 patients listed in Table II with blood sugar values in excess of 200 mg per cent, 14, or 50 per cent, died—about the mortality rate of the entire group of cases.

Diabetes Mellitus—Having thus established the fact that disturbances of carbohydrate metabolism of greater or less degree occur in a rather high percentage of patients with acute pancreatitis, I shall now consider true diabetes mellitus during the course of and following this disease. Although most text-books on surgery do not mention diabetes as a complication or sequela, such cases have appeared from time to time in the literature since the latter part of the nineteenth century. An attempt has been made to review all of these.

In Table II it will be seen that, excluding those cases of known pre-existing diabetes, this affection as a permanent disease follows 52 times in a series of some 2,855 cases of acute pancreatitis, an incidence of about 2 per cent. The fact that a certain number of these cases are reported, particularly because of the diabetes, is perhaps offset by cases which have not

TABLE

CASES OF DIABETES BEGINNING					
Author	Diagnosis	Sex	Age	Operation	Autopsy
CASES OF DEATH					
Benda and Stadelmann ¹⁰¹ (1896)	Acute pancreatitis	F	23	No	Yes
Neumann ¹⁰² (1904)	Acute hemorrhagic pancreatitis with almost total necrosis	F	24	Yes	Yes
Holten ¹⁰³ (1924)	Acute necrosis (total) of pancreas	F	48	No	Yes
Rodriguez ¹⁰⁶ (1924)	Acute pancreatitis	M	59	No	Yes
Tscherning ¹⁰⁷ (1925)	Hemorrhagic pancreatitis with severe necrosis	F	31	No	Yes
Bayer ³⁴ (1930)	Acute pancreatic necrosis	M	28	No	Yes
OTHER CASES OF DEATH					
Franke ¹⁰⁸ (1902)	Acute hemorrhagic pancreatitis	M	42	No	Yes
Bosanquet ¹⁰⁹ (1905)	Acute hemorrhagic pancreatitis	F	53	No	Yes
Caro and Winkler ¹¹⁰ (1918)	Acute hemorrhagic pancreatitis	M		No	Yes
Warfield ¹⁶ (1927)	Acute hemorrhagic pancreatitis	M	69	Yes	No
Warfield ¹⁶ (1927)	Acute pancreatic necrosis	M	50	Yes	Yes
Kerschner ³ (1929)	Acute pancreatic necrosis			Yes	
Kerschner ³ (1929)	Acute pancreatic necrosis			Yes	
Warren ³² (1930)	Acute pancreatitis	6 cases		?	Yes
CASES WITH SURVIVAL					
Brentano ¹¹¹ (1902)	Acute pancreatitis with subsequent subphrenic abscess	F	24	Yes	No
Peisner ¹¹ (1902)	Acute pancreatitis and hemorrhagic pseudocyst	F	28	Yes	No
Albu ¹¹³ (1911)	Acute pancreatitis with abscess	F	29	Yes	No
Vogel ¹¹⁴ (1924)	Acute pancreatitis			Yes	No
Matthaes ³⁷ (1931)	Acute pancreatitis with abscess	F		Yes	No
Bernhard ³⁸ (1931)	Acute pancreatic necrosis, subtotal in farct		32	Yes	No

been diagnosed either because of lack of interest or of systematic follow-up studies. In addition, some 10 similar cases have been collected from the earlier literature. Since I have found, during the period covered by Schmieden and Sebening's¹¹ report, only ten cases, it is apparent that eight of the 18 mentioned by these authors were collected through personal communications, or have failed to come to my attention in the literature. Altogether, then, there are some 62 cases of diabetes thought to be etiologically related to acute pancreatitis. The available data on these are assembled in Tables III, IV and V. Only cases in which the diagnosis was established at celiotomy or autopsy are included. Other more doubtful cases will be referred to subsequently.

III

DURING ACUTE PANCREATITIS

Onset of Diabetes	Character of Diabetes	Remarks
On admission	Died in coma after 1 wk	Was entirely well without symptoms of diabetes before acute illness
On admission	Died on tenth p o day, 1 day in coma	No definite proof of no preexisting diabetes, though presumably there was none Treated unsuccessfully with diet and soda bicarb
On admission	Died on third day of illness, in coma	Urine negative 5 wks before Insulin therapy
On admission	Died in 2 wks, in coma	Urine negative 6 wks before Insulin therapy
Within 2 wks	Died in coma, 6 days after adm	Urine negative 16 days before death Insulin therapy
Within 1 wk	Died in coma in 2 wks	Never any diabetic symptoms before Insulin therapy

DURING ACUTE ILLNESS

With onset of P -I *	Fulminating	Died 2 wks Never any symptoms of diabetes before P -I *
With onset of P -I *	Severe	Died in collapse with acidosis but without coma within 2 wks
On admission	Severe	Died within a few days Acidosis Urine negative during attack Questionable cholecystitis 1 yr before
On admission	Severe	Operation on twelfth day Death Presumably not a diabetic previously
Semicoma with onset of pain	Severe	Operation 1 mo after onset of P -I * Death in 10 days Had recently been examined and nothing abnormal found
	Severe	Died on fifteenth p o day
	Severe	Died on third p o day
'After the onset of symptoms'		No other details
* P -I represents present illness "		

OF ACUTE ILLNESS

11 days p o 6 wks after onset	Regulated with diet	Glycosuria decreased with diet, recurred again on mixed diet Large sequestrum (12x4x1½ cm)
Within 2 wks	Died in coma in 6 mos	Apparently no diabetes 2½ wks before during delivery Diet and soda bicarb Sequestrum (19x7x3 cm)
In 1 wk	Severe with acidosis	Urine negative on admission Followed for 2 yrs Diabetes did not exist before No other details
During acute illness	Fairly severe	Followed for 4 yrs Under constant supervision
Within 2 wks	Died in 4 yrs in coma	Passed small sequestra after operation

In Table III are listed 25 cases of diabetes beginning during the course of acute pancreatitis Six of these patients died within a short period in diabetic coma A number were treated with insulin Thirteen died during the acute illness with severe diabetes, though apparently not in coma No information concerning six of these³² is available Six patients whose diabetes began during the acute pancreatitis survived the acute illness Two of the six^{38, 112} died later in coma (six months and four years, respectively) Bren-
tano's¹¹¹ patient had not been followed long at the time of his report but apparently had a mild diabetes No details are given in Vogel's¹¹⁴ case The other two patients^{37, 113} were followed for two and four years, respectively, and had severe diabetes It should be mentioned that sequestration of the

pancreas was noted in three of these six patients who survived their acute illness

TABLE IV

CASES OF DIABETES BEGINNING SOON AFTER ACUTE PANCREATITIS

Author	Diagnosis	Sex	Age	Operation	Autopsy	Onset of Diabetes	Character of Diabetes	Remarks
Umber ¹¹⁶ (1925)	Severe acute pancreatitis Necrosis	F	27	Yes	No	1½ mos after operation	Managed well on insulin	Large sequestrum—almost all of pancreas Pt followed 2 yrs
Orthner ¹¹⁶ (1925)	Entirely infarcted hemorrhagic pancreas	F	28	Yes	No	Soon after discharge (discharged in 8 wks)	Managed well on insulin	Large sequestrum passed on sixteenth p o day
Ney ¹ (1929)	Lesser sac abscess from pancreatitis, cholecystitis, cholelithiasis	F	37	Yes	No	3 mos after operation	Mild	Urine neg on adm Transient glycosuria postoperatively
Felsenreich ⁴⁴ (1932)	Acute pancreatic necrosis Total infarct	F	36	Yes	No		Severe	No sequestrum

In Table IV are grouped four cases of diabetes with onset within a short period after recovery from acute pancreatitis. One patient had a mild diabetes,²¹ one a severe case,⁴⁷ two were managed well on insulin^{115, 116}. Two of the four had extensive sequestration of the pancreas.

In Table V are listed those cases of diabetes which ensued a year or more after acute pancreatitis and also a few in which the exact time relationship is not available. Altogether, there are 33 cases in which the diabetes came on from one to 22 years after the acute illness—an average of about seven years. In all the cases the pancreatitis was relatively severe, considerable sequestration was noted in four, and a long, persisting fistula in three instances. Six patients died with severe diabetes,^{21, 38, 45, 75, 111} no data are available as to the severity in 13 cases, four patients had mild diabetes, the remainder more or less severe.

It may be pointed out that practically all of the 62 patients listed had severe pancreatitis and that in the 43 who survived the acute episode, sequestration was fairly common, in at least 20 per cent.

In addition to the above cases there are reported about 19 cases of acute pancreatitis^{30, 43, 47, 55, 58, 71, 75, 114, 120 to 125} in patients known to have diabetes*. In one, the outcome is not stated¹¹⁴. One patient survived⁴³. The remaining 17 died, most of them in obvious diabetic coma. Not only was the disease almost always fatal, but in many instances it was extremely difficult to make the diagnosis of acute pancreatitis.

In addition to the cases reviewed above, Giott¹²⁶ is said to have had a patient who developed acute diabetes during the course of acute pancreatitis which persisted in a chronic form. I have been unable to examine his report. One of Umber's cases has been cited. He has seen diabetes develop in

* In two instances^{55, 71} it is not stated that the diabetes existed before the acute illness, though presumably it did.

16 other patients, among 38 with extensive pancreatic necrosis that he has observed¹²⁷ In these he suspected a preexisting diabetic tendency

Not included in the tabulated cases are a number in which the etiologic relationship of acute pancreatitis to diabetes depends upon the assumption that an initial abdominal crisis was due to the same process as a similar terminal one in which the diagnosis was definitely established, or upon the assumption that the diagnosis made at autopsy explained the initial part of a long continued illness Ellison¹²⁸ presented a patient whose diabetes began two months after the onset of abdominal complaints with jaundice The patient died about eight months later, and showed at autopsy a large pancreatic abscess with common duct obstruction Fleisch¹²⁹ reported two cases One was a female, age 27, who developed rather severe diabetes at the onset of an attack of abdominal pain, and who presented at autopsy, six months later, a large hemorrhagic cyst of the pancreas The other was a patient who developed diabetes about one month after the beginning of an acute illness, which was diagnosed at postmortem examination, six months later, as pancreatic abscess Ponfick¹³⁰ had a patient whose diabetes began with an acute illness quite similar to a fatal one terminating in diabetic coma Autopsy showed hemorrhagic pancreatitis Noiero's¹³¹ patient, likewise, developed diabetes five months after an acute illness quite similar to a subsequent fatal attack one year later which was diagnosed as acute pancreatitis and pancreatic cirrhosis The cirrhosis was a consequence of the initial attack There is fair reason to assume that a number of these cases may represent instances of diabetes due to acute pancreatitis

I have also not included several cases which might be termed temporary diabetes In 1902, Nash¹³² reported the case of a patient who was found to have acute pancreatitis and cholelithiasis on exploration and who had glycosuria when first seen and continued to excrete sugar for six months Seven months after operation his urine was free of sugar Hunt⁸⁵ and Whipple¹⁰¹ had patients with acute pancreatitis who required insulin therapy for hyperglycemia and glycosuria, and who recovered completely after a rather long time and remained well Brocq and Varangot⁸¹ reported the case of a patient who had abundant glycosuria postoperatively which recurred with acetoneuria when insulin was first discontinued, the patient was well at the end of three months Walzel²² had two patients in whom diabetes developed during acute pancreatitis, they refused operation and subsequently had relief from the diabetes following operative drainage of pseudocysts which had formed Sodeman¹³³ reported a similar instance of apparent disappearance of diabetes after operative treatment of a pancreatic cyst

Warfield,¹⁶ Wilder,¹³⁴ Stern,¹³⁵ Svartz,¹³⁶ Henningsen,¹³⁷ Mosenthal¹³⁸ and Sobel¹³⁹ have presented cases of diabetes which they are inclined to attribute to an acute pancreatitis not proved by celiotomy or autopsy I have not considered these cases in detail since there is more or less question as to the validity of the diagnosis A number of these authors feel that even mild, unrecognized cases of acute pancreatitis may either initiate diabetes

TABLE

CASES OF DIABETES BEGINNING ONE YEAR

Author	Diagnosis	Sex	Age	Operation	Autopsy	Onset of Diabetes
Brentano ¹¹¹ (1899) } Korte ^{5 117} (1898) } Rollmann ¹¹⁸ (1914)	Acute pancreatitis with abscess	F	48	Yes	Yes	1½ yrs
	Acute hemorrhagic pancreatitis with abscess	F	36	Yes	No	5 yrs
Vogel ¹¹⁴ (1924)	Acute pancreatitis	F	26	Yes	No	7 yrs
Vogel ¹¹⁴ (1924)	Acute pancreatitis	F		Yes	No	6 yrs
Dunn <i>et al</i> ¹¹⁹ (1926)	Acute pancreatitis	M	39	Yes	No	6 yrs
Dunn <i>et al</i> ¹¹⁹ (1926)	Acute pancreatitis	M	56	Yes	No	4 yrs
Von Redwitz ¹⁴ (1927)	Acute pancreatic necrosis	F		Yes	No	
Brutt ¹³ (1927)	Acute pancreatic necrosis			Yes	No	
Ney ²¹ (1929)	Acute hemorrhagic pancreatitis	F	38	Yes	No	3¼ yrs
Ney ¹ (1929)	Hemorrhagic cyst following pancreatitis	F	47	Yes	Yes	18 yrs
Ney ¹ (1929)	Acute pancreatitis	F	46	Yes	No	13 yrs
Ney ²¹ (1929)	Acute pancreatitis	M	35	Yes	No	22 yrs
Jorns ⁵ (1929)	Acute pancreatic necrosis	M	48	Yes	No	2½ yrs
Bernhard ³⁸ (1931)	Acute hemorrhagic pancreatitis		31	Yes		11 yrs
Bernhard ³⁸ (1931)	Acute pancreatic necrosis		52	Yes		8 yrs
Bernhard ³⁸ (1931)	Acute pancreatic necrosis		28	Yes	No	13 yrs
Bernhard ³⁸ (1931)	Acute pancreatic necrosis		29	Yes	No	1 yr
Joslin ^{7a} (1931) } Gurist ⁸ (1909) } Martens ⁴⁵ (1931)	Acute gangrenous pancreatitis	M	39	Yes	No	1½ yrs
	Acute necrosis			Yes	No	
Unger and Sostmann ⁴³ (1931)	Acute pancreatitis			Yes	No	
Lemieux ⁵⁴ (1932)	Acute hemorrhagic pancreatitis	F	22	Yes	No	1½ yrs
Downie ⁵³ (1932)	Acute pancreatitis	M	38	Yes	No	2 yrs
McWhorter ⁴⁸ (1932)	Acute pancreatitis			Yes	No	3 yrs
deTakats and MacKenzie ⁴⁹ (1932)	Acute necrosis			Yes	No	
deTakats and MacKenzie ⁴⁹ (1932)	Acute necrosis			Yes	No	
Schmieden and Sebening ¹¹	Acute necrosis	8 cases*		Yes	No	

or bring about an exacerbation of a preexisting diabetes Wilder,¹³⁴ Hirschfeld,¹⁴⁰ Patrick,¹⁴¹ Gundersen¹⁴² and Massa¹⁴³ have raised the question whether mumps may initiate diabetes through a concomitant pancreatitis. It is striking that in Patrick's review, as this author himself points out, those patients with definite diabetes following mumps had no abdominal pain to suggest acute pancreatitis.

Of great interest are those few available follow-up studies upon patients cured of acute pancreatitis. These are summarized in Table VI. One is at once impressed with the relatively high incidence of disturbance of carbohydrate metabolism. Of 161 patients followed, 14, or about 9 per cent, had diabetes. In addition, about 35 per cent of those studied had some alteration of glucose tolerance. Sebening⁸ and Brutt¹³ feel that a high percentage of patients have an abnormal glucose tolerance and that there is a tendency toward a return to normal as time passes.

V

OR MORE AFTER ACUTE PANCREATITIS

Character of Diabetes	Remarks
Severe Died in coma 8 yrs after operation	Large sequestrum
Severe	Urine negative at time of pancreatitis Followed 5 yrs
Rather severe	Urine negative at time of operation and 1 yr later
Moderately severe	Urine negative at time of acute illness
Well managed on insulin 30 u B I D Moderate	
Well managed on insulin 10 u B I D Mild	Trace of sugar found 2 yrs after operation
No details	Says blood sugar remained normal until patient became pregnant
Blood sugar 450 mg %	No other details
Mild Blood sugar 224 mg %	Had hyperglycemia during early part of course with glycosuria
Moderately severe Died 3 yrs later in coma (?) with fracture	
Moderate	Had negative urine during acute illness and during a recurrence 9 yrs later Had sequestration of pancreas
Mild	Transient glycosuria 1 mo postoperatively
No details	No glycosuria before
Died 7 yrs later with severe diabetes	Large sequestrum—pancreatic fistula for a long time
Died 1 yr later with severe diabetes and a carbuncle	Large sequestrum Fistula for 3 mos
Severe	
Severe	Fistula for 3 mos
Died in coma 4½ yrs later	Mother had diabetes No glycosuria during acute illness
Died of diabetes 4½ yrs after operation	
Mild	
Managed well on 10 u of insulin	
Required 70 u of insulin daily	No glycosuria before
No details	No glycosuria during acute illness
No details	Sugar-free before acute illness
No details	Sugar-free before acute illness
No details	* These 8 cases included in this series are not listed separately

As regards changes in carbohydrate metabolism and the very occasional occurrence of diabetes in other diseases of the pancreas, there are a number of reports available in the literature. Very closely related to the subject that has just been reviewed, and probably originating from the same initial lesion, are the cases of pancreatic pseudocysts and diabetes. Beadle¹⁴⁴ and Sims¹⁴⁵ have presented cases and cited a few others from the literature. Bernhard¹⁴⁶ has also discussed the relationship between pancreatic cysts and diabetes. Wells¹⁴⁷ reported a case of diabetes following posttraumatic calcification of the pancreas and cited another case reported by Grund. Labbe¹⁴⁸ has presented a few cases of pancreatic lithiasis and diabetes and mentioned a few others from the literature. Diabetes apparently following carcinoma of the pancreas is quite rare.^{149,151} Sweeney¹⁵² reported a case of subacute pancreatitis in a man with a strongly diabetic family history who developed a temporary diabetes with his illness. Others,^{77, 153, 154} have dis-

cussed carbohydrate metabolism changes in chronic pancreatitis. The possible rôle of pancreatic involvement in some cases of biliary tract disease and diabetes has been discussed by several authors^{155, 156}

TABLE VI

FOLLOW-UP STUDIES AFTER ACUTE PANCREATITIS

Author	No of Cases Studied	Time Between Acute Illness and Follow-Up Study in Years	No With Abnormal Glucose Tolerance But Not True Diabetes	No With Diabetes	Comments
Sebening ⁸ (1927)	21	½-17	All studied 6 months after operation *	0	* Usually normal when studied a year or more after operation
Brutt ¹³ (1927)	20		Most cases studied shortly after acute illness	1	None had high blood sugar except the instance of true diabetes
Ney ¹ (1929)	13	¼-23	3*	5	* 2 spilled sugar in urine during test
Tammann ⁴ (1929)	12		6*	0	5 had slightly elevated fasting blood sugar (128-153 mg) * 2 spilled sugar in urine during test
Jorns ⁵ (1929)	7	½-13½	5	1	
Stocker ³⁶ (1930)	5	Less than 3	*	0	* All had elevated fasting blood sugar. No further details
Bernhard ³⁸ (1931)	50		5*	5	* 25 cases studied. 4 had glycosuria during test
Unger and Sostmann ⁴³ (1931)	16		5	1*	* Another case of diabetes had existed at time of operation
Downie ⁵³ (1932)	11		2	1	
deKlimko ⁷³ (1936)	6	½-5	3*	0	* Slight changes

Although I have not reviewed the entire literature concerning the diseases mentioned above, it seems apparent that they are associated much less commonly with diabetes than is acute pancreatitis. When one considers the relative severity of pathologic damage in the various conditions, this observation is as might be expected. Furthermore, since these disease processes have a more insidious onset than acute pancreatitis, it is not possible to ascribe to them the causative rôle in the production of diabetes with the relative certainty that can be felt when diabetes ensues after such an abrupt and striking crisis as acute pancreatitis.

The fact has been mentioned that certain authors have felt that mild cases of pancreatitis may result in diabetes. On the other hand, most of those who have had an opportunity to study altered carbohydrate metabolism and diabetes during and following proved cases of acute pancreatitis are impressed with the severity of the pancreatic necrosis in these cases. In general, it seems apparent that these disturbances are due to damage of the islet tissue, though not necessarily of such a nature as to leave anatomic landmarks of the injury. There are no data available to suggest that the destruction of the pancreas is predominantly in one part of the organ or another in those instances in which diabetes has followed pancreatitis, but rather that in most of them there has been almost complete necrosis of the organ. There has

been no consistent diminution in the number of islets of Langerhans or in their histologic appearance, although these observations have been made. Interestingly enough, Koite,⁵ who reported one of the early cases, doubted, once he saw the pathologic material at autopsy, that the diabetes had been due to the pancreatic disease. In this case the head was somewhat enlarged, and the body and tail showed to a large extent replacement by fibrosis. Sebening⁸ emphasizes the importance of loss of pancreatic tissue during the acute illness in the production of diabetes. Bernhard³⁸ also feels that the severity of the necrosis, the extent of sequestration, and the persistence of pancreatic fistulae are important factors. Jorns²³ stresses the possible rôle of ensuing chronic pancreatitis. Tammann²⁴ feels that age is an important factor and that patients with acute pancreatitis who are over 40 run a greater risk of developing diabetes. Bernhard³⁸ presents data suggesting that this is not true, and certainly it does not seem apparent from the present survey. The importance of familial predisposition to diabetes, mentioned by Umber¹²⁷ and Sweeney,¹⁵² does not seem of great significance in the cases reviewed.

Discussion—In considering acute pancreatitis and diabetes, one may legitimately ask "What proof have we of a causal relationship?" Diabetes may make its appearance in any decade of life. It is commonly first diagnosed during some acute illness, whether this is an upper respiratory infection, a carbuncle, or some other disease.

It appears obvious, however, that all the evidence speaks in favor of the pancreatic damage as the etiologic agent. In the first place, disturbances of carbohydrate metabolism occur with great frequency during the course of acute pancreatitis. Glycosuria is probably present in 10 to 12 per cent of all cases at one time or another during the acute illness. Hyperglycemia is apparently present with considerable regularity, and altered glucose tolerance, it seems, may be demonstrated in an even higher percentage of cases. Those instances of definite diabetes coming on abruptly during or shortly after the acute illness, such as my case and those collected in Table III, are very impressive. Perhaps little significance could be attached to the cases of diabetes ensuing one year or more after acute pancreatic necrosis, were it not for the fact that, in careful follow-up studies, not only is diabetes found in a significant percentage of cases, but lesser grades of impaired glucose tolerance are observed in a much larger proportion. Altogether the pathogenesis of this type of diabetes seems well established.

As to the factors involved in the production of diabetes, the most striking is that, practically without exception, the cases of diabetes following proved acute pancreatitis have developed after a very severe pancreatitis, generally with widespread necrosis of the organ. Extensive pancreatic sequestration seems to increase the likelihood of diabetes. The fact that, anatomically, acute pancreatitis affects predominantly the acinous tissue rather than the islets of Langerhans is of little concern. Instances are numerous of the so-called idiopathic diabetes in which no anatomic change can be demonstrated in the islet tissue.

Undoubtedly, there are many attacks of mild pancreatitis that escape recognition. It is unlikely, in view of the severity of the necrosis in the proved cases, that these mild cases are responsible for the development of diabetes, though it is possible that such mild attacks may cause exacerbations of preexisting diabetes.

As regards the importance of these findings in the surgical management of acute pancreatitis, the indications are clear. Obviously, every patient should have a complete urine examination before operation. The occasional occurrence of glycosuria may be suggestive, though this finding occurs too infrequently to be of great diagnostic aid. As long as one adheres to the belief that surgical drainage is the treatment of choice, as I do, there may not always be time for extensive blood studies. Each suspected case of acute pancreatitis, however, should have blood drawn for an immediate or subsequent blood sugar examination, and in those instances in which operation must be delayed a few hours because of shock or other circumstance, it will not be amiss to make a glucose tolerance test. Certainly, these studies should be made in instances of suspected mild acute pancreatitis. It will only be through thus accumulating a large amount of data that the present conception of the very high incidence of hyperglycemia and decreased glucose tolerance can be substantiated and the diagnostic value of these procedures confirmed. Likewise, further study will settle the question as to the prognostic importance of these observations. Postoperatively, the urine and blood sugar should be tested frequently and a glucose tolerance test should be made from time to time. Appropriate dietary or insulin therapy should be instituted where indicated. Rich¹²⁵ has raised the question as to the possible enhancement of the pancreatic damage through the use of intravenous glucose, because of its action in stimulating secretion of the pancreatic enzymes. Lewis¹⁵⁷ and Wangenstein¹⁵⁸ have, consequently, suggested that glucose should be given sparingly. It may prove of help to avoid a high carbohydrate diet and intravenous administration of glucose unless they are covered by insulin. Those patients who survive their acute illness must be warned to return for frequent follow-up studies. Perhaps early recognition and proper dietary regimen may avert a serious diabetes in those patients showing a mild disturbance of carbohydrate regulation.

SUMMARY AND CONCLUSIONS

(1) A case of severe diabetes mellitus developing in the course of acute hemorrhagic pancreatitis is presented. Other instances of altered carbohydrate metabolism in acute pancreatitis are reported.

(2) The literature concerning changes in carbohydrate metabolism in acute pancreatitis and diabetes as a complication or sequela is discussed.

(3) It is pointed out that glycosuria occurs in about 11 per cent of patients with acute pancreatitis, and that hyperglycemia and decreased glucose tolerance occur in a much greater proportion of cases. The diagnostic importance of the latter tests is discussed.

(4) Diabetes may develop during acute pancreatitis. It may terminate rapidly in coma, or the patient may survive with a persistent diabetes of greater or less severity. It may ensue after a few months or many years. At least 2 per cent of all patients with severe acute pancreatitis develop diabetes, and, of those surviving the acute illness, from 3 to 10 per cent develop this malady. A much larger percentage of surviving patients will have milder grades of altered carbohydrate metabolism. It seems unlikely that mild cases of acute pancreatitis result in diabetes.

(5) It is suggested that these features of the disease be kept in mind in the management of acute pancreatitis, and that systematic follow-up studies be made.

BIBLIOGRAPHY

- ¹ Fitz, R. Acute Pancreatitis. *Boston Med and Surg Jour*, **120**, 180-187, 205-207, 1889.
- ² Fitz, R. Acute Pancreatitis. *Med Rec*, **35**, 197-204, 225-231, 253-261, 1889.
- ³ Atkinson, I. E. Notes on a Case of Suppurative Pancreatitis with Report of Necropsy. *J A M A*, **24**, 999-1002, 1895.
- ⁴ Harley, G. Complete Obstruction to the Bile and Pancreatic Ducts. *Trans Path Soc Lond*, **13**, 118-119, 1862.
- ⁵ Korte, W. Die chirurgische Behandlung der acuten Pankreatitis. *Arch f klin Chir*, **96**, 557-615, 1911.
- ⁶ Egdaahl, A. A Review of One Hundred and Five Reported Cases of Acute Pancreatitis, with Special Reference to Etiology, with Report of Two Cases. *Bull Johns Hopkins Hosp*, **18**, 130-136, 1907.
- ⁷ Guleke, N. Cited by Walzel.²²
- ⁸ Sebening, W. Folgezustände nach akuter Pankreasnekrose. *Med Klin*, **23**, 551-556, 1927.
- ⁹ Bernhard, F. Die Beziehungen zwischen der Erkrankungen der Gallenwege und dem Auftreten der akuten Pankreasnekrose und Beobachtungen über die diagnostischen Hilfsmittel zur Erkennung der akuten Pankreasveränderungen. *Deutsch Ztschr f Chir*, **23**, 1-30, 1931.
- ¹⁰ Mahner, H. Erfahrungen mit akuten Pankreaserkrankungen. *Arch f klin Chir*, **187**, 691-704, 1937.
- ¹¹ Schmieden, V., and Sebening, W. Chirurgie der Pankreas. *Arch f klin Chir*, **148**, 319-387, 1927.
- ¹² Schmieden, V., and Sebening, W. Surgery of the Pancreas, with Especial Consideration of Acute Pancreatic Necrosis. *Surg, Gynec and Obstet*, **46**, 735-751, 1928.
- ¹³ Brutt. *Arch f klin Chir*, **148**, 72-73, 1927.
- ¹⁴ Von Redwitz. *Arch f klin Chir*, **148**, 82-83, 1927.
- ¹⁵ Kummer. Pancreatite aigue hemorrhagique. *Schweiz med Wchnschr*, **57**, 525, 1927.
- ¹⁶ Warfield, L. M. Acute Pancreatitis Followed by Diabetes. *J A M A*, **89**, 654-658, 1927.
- ¹⁷ Watkins, R. P. Acute Pancreatitis. *New Eng Jour Med*, **198**, 605-609, 1928.
- ¹⁸ Delmore, J. L. Acute Pancreatitis. *Minnesota Med*, **11**, 80-82, 1928.
- ¹⁹ Kreiner, W. Über weitere Fälle von Pankreatitis mit Hyperglykämie. *Zentralbl f Chir*, **55**, 1219-1222, 1928.
- ²⁰ GRANT, J. W. G. Acute Necrosis of the Pancreas. *Brit Med Jour*, **1**, 1101-1103, 1928.
- ²¹ Ney, H. Über das Auftreten von Störungen im Kohlehydratabbau und von Diabetes mellitus nach Erkrankungen des Pankreas. *Arch f klin Chir*, **154**, 378-397, 1929.

- ²² Walzel, P Zur Diagnose und Therapie der akuten Pankreasnekrose Beitr z klin Chir, 147, 1-13, 1929
- ⁻³ Kerschner, F Über akute Pankreasnekrose Beitr z klin Chir, 147, 14-27, 1929
- ²¹ Tammann, H Über Ergebnisse des operativen Behandlung der akuten Pankreasnekrose nach dem Material der Göttinger Chirurgischen Klinik in den Jahren 1912 bis 1929 Beitr z klin Chir, 148, 49-66, 1929
- ²⁵ Jorns, J Experimentelle und klinische Beiträge zur Pathologie der Langerhanschen Inseln des Pankreas Beitr z klin Chir, 146, 269-318, 1929
- ²⁶ Linder, W, and Morse, L J Acute Pancreatitis An Analysis of Eighty-eight Cases with Especial Reference to Diagnosis ANNALS OF SURGERY, 90, 357-366, 1929
- ²⁷ Olds, W H Acute Pancreatitis California and West Med, 30, 159-163, 1929
- ²⁸ Simon, H Zum Krankheitsbild der akuten Pankreasnekrose Beitr z klin Chir, 148, 279-282, 1929
- ⁻⁹ Kramer Zur Kasuistik der Pankreaserkrankungen (akute Pankreatitis) München med Wchnschr, 76, 746-747, 1929
- ⁻⁰ Cullen, T S, and Friedenwald, J Acute and Chronic Pancreatitis Clinical Observations Arch Surg, 15, 1-29, 1929
- ³¹ Oehler, J Zur Pankreasnekrose Deutsch med Wchnschr, 55, 866-868, 1929
- ³² Warren, S The Pathology of Diabetes Mellitus Lea and Febiger, Philadelphia, 1930
- ⁻ Eliason, E L, and North, J P Acute Pancreatitis Surg, Gynec and Obstet, 51, 183-189, 1930
- ³⁴ Bayer, L M Six Fatal Cases of Diabetic Acidosis, with Special Reference to the Occurrence of Acute Pancreatic Necrosis in One and Severe Nephrosis in Another Am Jour Med Sci, 179, 671-683, 1930
- ³⁵ Weeden, W M Acute Pancreatitis with Report of Twelve Cases Am Jour Surg, 8, 1286-1289, 1930
- ³⁶ Stocker, H Ein Beitrag zur Statistik und Klinik der akuten Pankreasnekrose Arch f klin Chir, 156, 84-95, 1930
- ⁻⁷ Matthes Untersuchungen der Pankreasfunktion nach überstandener Pankreatitis Arch f klin Chir, 164, 266-271, 1931
- ⁻⁸ Bernhard, F Das Auftreten des Diabetes mellitus nach akuten Pankreaserkrankungen Klin Wchnschr, 10, 632-637, 1931
- ³⁹ Hopkins, P E Acute Pancreatitis Illinois Med Jour, 60, 109-113, 1931
- ⁴⁰ Dunn, J H Acute Pancreatitis Kentucky Med Jour, 29, 564-565, 1931
- ⁴¹ Mackechmie, H N, and Olsen, E C Acute Pancreatitis Surg Clin North Amer, 11, 181-182, 1931
- ⁴² Grant, J W G Acute Haemorrhagic Pancreatitis Brit Med Jour, 2, 1084-1086, 1931
- ⁴³ Unger, E, and Sostmann, H Erfahrungen an 100 Fällen akuter Pankreaserkrankungen Med Klin, 27, 198-200, 1931
- ⁴⁴ Kappis, M Konservative oder operative Behandlung der akuten Pankreatitis? Med Klin, 27, 842-843, 1931
- ¹ Martens, M Über akute Pankreasnekrose Med Klin, 27, 155-159, 1931
- ⁴⁶ Rich, G F Acute Pancreatic Necrosis New Zealand Med Jour, 31, 254-262, 1932
- ⁴⁷ Felsenreich, F Klinik der akuten und subakuten Pankreasnekrose Arch f klin Chir, 168, 307-348, 1932
- ⁴⁸ McWhorter, G L Acute Pancreatitis Arch Surg, 25, 958-990, 1932
- ⁴⁹ deTakats, G, and MacKenzie, W D Acute Pancreatic Necrosis and Its Sequelae ANNALS OF SURGERY, 96, 418-440, 1932
- ⁻⁰ Jones, C R Acute Pancreatitis Am Jour Surg, 15, 510-514, 1932
- ⁵¹ Lyall, A Acute Hemorrhagic Pancreatitis Brit Med Jour, 2, 146, 1932
- ⁵² Quick, B Acute Pancreatitis Australian and New Zealand Jour Surg, 2, 115-132, 1932

- ⁵³ Downie, E Observations on Glucose Tolerance in Cases of Recovered Pancreatitis Australian and New Zealand Jour Surg, 2, 141-151, 1932
- ⁵⁴ Lemieux, R Un cas de diabete tardif consecutif a une pancreatite hemorrhagique Bull Soc med d hôp, Univ de Quebec, 33, 316-321, 1932
- ⁵⁵ Truesdale, P E Acute Pancreatitis, with a Review of Fifty-four Operative Cases New Eng Jour Med, 210, 66, 1934
- ⁵⁶ Haynes, H H A New Surgical Procedure for Acute Pancreatitis Arch Surg, 26, 288-294, 1933
- ⁵⁷ Hartlieb, G Neuere Arbeiten uber die operative Behandlung der akuten Pankreasnekrose bzw der akuten Pankreatitis Beitr z klin Chir, 157, 539-557, 1933
- ⁵⁸ Jacobovici, J Quatorze cas de pancreatite aigue Bull et mem Soc Nat de Chir, 59, 613-620, 1933
- ⁵⁹ Thomas, T T Acute Pancreatitis Med Rec, 137, 89-93, 1933
- ⁶⁰ Finney, J M T Pancreatic Emergencies ANNALS OF SURGERY, 98, 750-759, 1933
- ⁶¹ Rienhoff, W F, and Lewis, D Surgical Affections of the Pancreas, etc Bull Johns Hopkins Hosp, 54, 386-429, 1934
- ⁶² Koster, H, and Kasman, L P Acute Pancreatitis Arch Surg, 29, 1014-1023, 1934
- ⁶³ Horine, C F Acute Pancreatitis ANNALS OF SURGERY, 99, 301-306, 1934
- ⁶⁴ Harve, P Acute Pancreatitis Liverpool Med-Chir Jour, 43, 105-119, 1935
- ⁶⁵ Donald, D C Acute Pancreatic Necrosis J M A, Alabama, 5, 47-53, 1935
- ⁶⁶ LeSage, A, and LeSage, J R A Acute Pancreatitis, a Clinical and Pathological Study, with Personal Observations Am Jour Digest Dis, 2, 449-459, 1935
- ⁶⁷ Henderson, F F, and King, E S A Acute Pancreatitis Arch Surg, 30, 1049-1057, 1935
- ⁶⁸ Dobbs, R H Acute Pancreatitis in Childhood Lancet, 2, 989-991, 1935
- ⁶⁹ Huet, M Sequelles de la pancreatite hemorrhagique, valeur du drainage des voies biliaires apparemment saines Bull et mem Soc Nat de Chir, 61, 686-694, 1935
- ⁷⁰ Douglas, J Diseases of the Pancreas, Especially Acute Pancreatitis and Its Treatment Am Jour Digest Dis, 1, 871-879, 1935
- ⁷¹ Douglas, J Acute Surgical Lesions of the Pancreas ANNALS OF SURGERY, 98, 909-918, 1933
- ⁷² Mendelssohn, E Acute Pancreatitis West Jour Surg, 44, 474-478, 1936
- ⁷³ deKlimko, D The Surgical Treatment of Acute Pancreatitis Surg, Gynec and Obstet, 63, 89-95, 1936
- ⁷⁴ Rochet, P Pancreatitis aigues Lyon Chir, 33, 720-727, 1936
- ⁷⁵ Joslin, E P The Treatment of Diabetes Mellitus Lea and Febiger, Philadelphia, 1937
- ⁷⁶ Jurist, L Acute Gangrenous Pancreatitis Am Jour Med Sci, 138, 180-188, 1909
- ⁷⁷ Weir, J F Pancreatitis Med Clin North Amer, 21, 675-689, 1937
- ⁷⁸ Gatewood Acute and Chronic Pancreatitis Surg Clin North Amer, 172, 473-487, 1937
- ⁷⁹ Sedgley, F R Pancreatitis, Acute and Chronic, with Case Reports Med Bull Vet Admin, 14, 151-156, 1937
- ⁸⁰ Trasoff, A, and Scarf, M Acute Pancreatitis, a Medical Problem Am Jour Med Sci, 194, 470-474, 1937
- ⁸¹ Brocq, P, and Varangot, J Les modifications de la glycemie dans la necrose aigue du pancreas Jour de Chir, 49, 177-220, 1937
- ⁸² Kufferath, W, and Volkmann, K Zur Frage der Behandlung der akuten Pankreatitis Med Klin, 34, 356-359, 1938
- ⁸³ Beck, D Acute Pancreatitis A Review and a Report of Ten Verified Cases Jour Mt Sinai Hosp, 4, 895-922, 1938
- ⁸⁴ Dunlop, G R, and Hunt, E L Acute Pancreatitis New Eng Jour Med, 218, 376-385, 1938

- ⁸⁵ Hunt, E L Pancreatitis, Acute and Subacute Some Special Problems in Post-operative Care *New Eng Jour Med*, 198, 610-616, 1928
- ⁸⁶ Abell, I Acute Pancreatitis *Surg, Gynec and Obstet*, 66, 348-353, 1938
- ⁸⁷ Calzavara, D Die akute hochgradige Hyperglykämie als charakterisches Frühsymptom bei experimentell erzeugten Pankreasnekrosen *Zentralbl f Chir*, 51, 1405, 1924
- ⁸⁸ Fiessinger, N Pancreatites aiguës et hémorragiques *Rev gen de clin et de therap*, 49, 305-310, 1935
- ⁸⁹ Bernhard, F Über die Hyperglykämie bei akuten Pankreaserkrankungen *Deutsch Ztschr f Chir*, 212, 209-216, 1928
- ⁹⁰ Brody, W, and Custer, R P Acute Hemorrhagic Necrosis of the Pancreas *Am Jour Med Sci*, 184, 389-399, 1932
- ⁹¹ Goldman, C H Beobachtungen über Pankreatitis *Deutsch med Wchnschr*, 58, 701, 1832
- ⁹² Gabrielle, S Le variazioni della glicemia in corso di pancreatite acute e croniche *Ann ital di chir*, 17, 473-489, 1933
- ⁹³ Wildegans, H Die funktionelle Pankreasdiagnostik *Chirurg*, 1, 343-349, 1928-1929
- ⁹⁴ Wildegans, H Abwartende oder primär chirurgische Behandlung des akuten Pankreasnekrose *Chirurg*, 8, 597-604, 1936
- ⁹⁵ Cole, W H Acute Pancreatitis, with Special Reference to Pathogenesis and the Diagnostic Value of the Blood Amylase Test *Am Jour Surg*, 40, 245-259, 1938
- ⁹⁶ Krotoske Cited by deTakats and MacKenzie⁴⁹
- ⁹⁷ Brocq, P Les pancreatites aiguës chirurgicales *Masson et Cie, Paris*, 1926
- ⁹⁸ Bernhard, F Ursachen, Diagnose und Behandlung der akuten Pankreaserkrankungen *Deutsch med Wchnschr*, 61, 667-669, 1935
- ⁹⁹ Mikkelsen, O Pancreatitis acuta *Acta chir Scandinav*, 75, 373-415, 1934
- ¹⁰⁰ Troissier, J, Bariety, M, and Gabriel, P Troubles de la regulation glycémique dans la pancreatite hémorragique (Instabilité de la glycémie et hypoglycémie alimentaire) *Bull et mem Soc d hop de Paris*, 50, 861-871, 1934
- ¹⁰¹ Speese, J, Revised by A O Whipple *Surgery of the Pancreas Chap 8, 5, Nelson Loose-Leaf Living Surgery Thomas Nelson & Sons, New York*, 1937
- ¹⁰² Neumann, A Zur Diagnose der Pankreaserkrankungen *Deutsch Ztschr f Chir*, 74, 298-311, 1904
- ¹⁰³ Geinitz, R Hyperglykämie bei akuter Pankreasnekrose *Zentralbl f Chir*, 33, 2069-2070, 1928
- ¹⁰⁴ Benda, C, and Stadelmann *Deutsch med Wchnschr*, 22, Vereins-Beilage, 138, August 6, 1896
- ¹⁰⁵ Holten, C Akute Pankreasnekrose Coma diabeticum *Deutsch med Wchnschr*, 8, 237-238, 1924
- ¹⁰⁶ Rodriguez, J Acute Pancreatitis with Fat Necrosis, Complicated by Diabetic Coma *J A M A*, 82, 203-204, 1924
- ¹⁰⁷ Tscherning, R Zur Klinik der Pankreasnekrose *Arch f Verdauungskr*, 35, 103-107, 1925
- ¹⁰⁸ Franke, K Über einen akutenverlaufenden Fall von Diabetes mellitus veranlasst durch Pankreasverletzung (Pankreatitis haemorrhagica) *Diss, Leipzig*, 1902
- ¹⁰⁹ Bosanquet, W C Some Considerations on the Nature of Diabetes Mellitus *Lancet*, 1, 977-982, 1905
- ¹¹⁰ Caro and Winkler Ausgedehnte hämorrhagische Pankreasnekrose und Diabetes mit Acidose *Deutsch Arch f klin Med*, 125, 147-159, 1918
- ¹¹¹ Brentano, A Subphrenischer Abscess nach Pankreasnekrose *Zentralbl f Chir*, 26, 1357-1358, 1899
- ¹¹² Peisner, E Zur Kenntnis der Pankreasnekrose *Deutsch Ztschr f Chir*, 65, 302, 1902

- ¹¹³ Albu, A Beiträge zur Diagnostik des inneren und chirurgischen Pankreasne-
krankungen Samml Zwangl Abhandl a d Geb d Verdauungskr, 3, C Marhold,
Halle, 1911
- ¹¹⁴ Vogel, R Erfahrungen über Pankreatitis acuta Deutsch Ztschr f Chir, 185,
71-92, 1924
- ¹¹⁵ Umber Entwicklung eines insularen Diabetes als Folge einer schweren Pankreasne-
krose Zentralbl f Chir, 522, 1819, 1925
- ¹¹⁶ Orthner, R Monatsversammlung der Ärzte von Oberösterreich Linz vom 1 Juli,
1925 Abstract in Wien klin Wchnschr, 38, 1050, 1925
- ¹¹⁷ Korte, W Die chirurgischen Krankheiten und die Verletzungen des Pankreas
Deutsch Chir, Nr 45, D F Enke, Stuttgart, 1898
- ¹¹⁸ Rollmann Pancreatitis acuta Deutsch Ztschr f Chir, 128, 86-129, 1914
- ¹¹⁹ Dunn, J P S, Vatcher, S, and Woodwork, A S Diabetes as Sequela to Acute
Pancreatitis Lancet, 1, 595-597, 1926
- ¹²⁰ Schott, E Pankreasnekrose beim Diabetiker—Koma Insulin München med
Wchnschr, 73, 1185-1187, 1926
- ¹²¹ Schufftan, S Über den Einfluss akuter Pankreaserkrankungen auf den Diabetes
mellitus Diss, Berlin, 1927
- ¹²² Cabot (Case 16282) Acidosis and Coma New Eng Jour Med, 203, 82-85, 1930
- ¹²³ Foord, A G, and Brown, B D Acute Interstitial Pancreatitis in Two Cases of
Diabetic Coma Am Jour Med Sci, 180, 676-681, 1930
- ¹²⁴ Root, H F Diabetic Coma and Acute Pancreatitis with Fatty Livers J A M A,
108, 777-780, 1937
- ¹²⁵ Rich, A R, and Duff, G L Experimental and Pathological Studies on the Patho-
genesis of Acute Haemorrhagic Pancreatitis Bull Johns Hopkins Hosp, 58,
212-259, 1936
- ¹²⁶ Grott Cited by Joslin ⁷⁵
- ¹²⁷ Umber, F Der Diabetes in seiner Beziehung zu Traumen und zum Berufsleben
Med Welt, 9, 889-891, 1935
- ¹²⁸ Frison, V Pancreatite suppuree Ictere par retention de bile Diabete sucré Mort
Marseille med, 12, 257-265, 1875
- ¹²⁹ Frerichs, F T V Über den Diabetes A Hirschwald, Berlin, 1884
- ¹³⁰ Ponfick, E Diabetes und Fettgewebsnekrose des Pankreas Verhandl der Deutsch
pathol Gesellsch, V Tagung, 4-5, 133-150, 1901-1902
- ¹³¹ Norero Diabete gras au cours d'une pancreatite aigue partielle Arch d mal de
l'appar digest, 7, 86-95, 1913
- ¹³² Nash, W G Acute Pancreatitis with Cholelithiasis and Glycosuria, Cholecystotomy,
Recovery Lancet, 2, 1192-1193, 1902
- ¹³³ Sodeman, W A A Case of Cystic Disease of the Pancreas with Apparent Dis-
appearance of Diabetes Following Operation New Orleans Med and Surg Jour,
90, 543-549, 1938
- ¹³⁴ Wilder Cited by Warfield ¹⁶
- ¹³⁵ Stern, M Fall von Diabetes gravis mit Pankreatitisschuben Schweiz med
Wchnschr, 11, 63-64, 1930
- ¹³⁶ Svartz, N Recidivating Pancreatitis and Diabetes Acta med Scandinav, 77, 198-
210, 1931
- ¹³⁷ Henningsen, E J Pancreatitis acuta med udtalde diabetesymptome Hospitalstid,
77, 353-364, 1934
- ¹³⁸ Mosenthal, H O Pancreatitis and Diabetes Ann Int Med, 11, 1001-1013, 1937
- ¹³⁹ Sobel, S P Two cases of Acute Pancreatitis One Complicated by Diabetes Mellitus
Med Rec, 147, 11-14, 1938
- ¹⁴⁰ Hirschfeld, F Über infektiöse Entstehung der chronischen Pankreatitis und des
Diabetes Berl klin Wchnschr, 45, 537-542 1908
- ¹⁴¹ Patrick, H Acute Diabetes Following Mumps Brit Med Jour, 2, 802, 1924

- ¹⁴² Gundersen, E Is Diabetes of Infectious Origin? *J Infect Dis*, **1**, 197-202, 1927
- ¹⁴³ Massa, M Pancreatite parotitica e diabete giovanile *Gazz d Osp*, **50**, 168-173, 1929
- ¹⁴⁴ Beadle, O A A Case of Pancreatic Cyst Associated with Diabetes *Guy's Hosp Rep*, **78**, 82-89, 1928
- ¹⁴⁵ Simsch, G Diabetes mellitus, im Anschluss an Cholecystitis, Pankreatitis und operativ behandelte Pankreaspseudozyste *Deutsch med Wchnschr*, **2**, 1641, 1932
- ¹⁴⁶ Bernhard, F Uber Pankreascysten, mit besonderer Berucksichtigung ihrer atologie, sowie des Dauerfolges der operativen Behandlung, nebst Untersuchungen uber die Beziehungen zwischen den Pankreascysten und dem spateren Auftreten eines Diabetes mellitus *Deutsch Ztschr f Chir*, **236**, 281-299, 1932
- ¹⁴⁷ Wells, H G Posttraumatic Calcification of the Pancreas, with Diabetes *Am Jour Med Sci*, **164**, 479-492, 1922
- ¹⁴⁸ Labbe, M Lithiase pancreatique et diabete *Bull et mem Soc med d Hop d Paris*, **52**, 594-598, 1936
- ¹⁴⁹ Urmy, T V, Jones, C K, and Wood, J C A Case of Diabetes Mellitus and Fatty Diarrhea Due to Carcinoma of the Pancreas *Am Jour Med Sci*, **182**, 662-675, 1931
- ¹⁵⁰ Pygott, F, and Osborn, H Pancreatic Cancer with Diabetes *Lancet*, **1**, 1461-1462, 1937
- ¹⁵¹ Grott, J V Glycosurie et diabete dans le cancer du pancreas *Arch d mal de l'app digestif*, **28**, 361-379, 1938
- ¹⁵² Sweeney, J E Pancreatitis and Diabetes Mellitus *Am Jour Med Sci*, **15**, 508-510, 1931
- ¹⁵³ Brinck, J Hyper und Hypoglykamie bei Pankreatitis *Ztschr f klin Chir*, **127**, 488-498, 1935
- ¹⁵⁴ Grott, J V Pancreatite chronique latente (Observations cliniques) *Arch d mal de l'app digestif*, **29**, 57-73, 1939
- ¹⁵⁵ Rodescu, L A A propos de deux cas de diabete postlithiasique, dont un coincident avec un pancreatite aigue *Vie med*, **14**, 783-786, 1933
- ¹⁵⁶ Chiray, M, Pavel, I, and LeSage, J Diabete et cholecystite *Presse med*, **402**, 1365-1367, 1932
- ¹⁵⁷ Lewis, D Acute Hemorrhagic Pancreatitis Causes of, Symptoms and Treatment *New York State Jour Med*, **36**, 1015-1019, 1936
- ¹⁵⁸ Wangensteen, O H Surgical Diseases of the Pancreas, with Special Reference to Cysts, Acute Pancreatic Necrosis, and Hypertension *Minnesota Med*, **20**, 566-576, 1937

INDICATIONS FOR LOBECTOMY AND PNEUMONECTOMY IN PULMONARY TUBERCULOSIS*

PAUL C SAMSON, M D

OAKLAND, CALIF

PULMONARY RESECTION as a treatment for tuberculosis may be classified in two separate periods. In 1881, Block¹ performed unsuccessfully what probably was the first planned pulmonary resection for tuberculosis. From 1881 to 1895, cases were reported by Ruggi,² Tuffei,³ and others. Tuffei believed that pulmonary resection should be employed when the tuberculosis was localized. He felt that by removal of the primary focus, a spread of the disease might be prevented.

No cases were reported from 1895 to 1934. Probably the poor results previously obtained discouraged surgeons. In addition, the acceptance of collapse therapy was becoming more widespread and the efficiency of thoracoplasty was increasing.

The second period began in 1934. In that year Freedlander⁴ performed a successful right upper lobe lobectomy for a tuberculous cavity that could not be closed by pneumothorax. In 1938, Jones and Dolley⁵ reported their series of two lobectomies and three pneumonectomies performed in tuberculous patients. They were the first to suggest some of the criteria for planned pulmonary resection in tuberculosis. Scattered cases presented by Beye,⁶ Eloessei,⁷ O'Brien,⁸ Blunn,⁹ Rienhoff,¹⁰ Lindskog,¹¹ Crafoord,¹² and others have brought the total number now reported⁵ in the literature to 22. In several of these, tuberculosis was an unexpected microscopic diagnosis following the removal of a lobe or a lung for suppuration.

Many thoracic surgeons now feel that lobectomy and pneumonectomy probably have a definite place in the surgery of pulmonary tuberculosis. As is usually the case with procedures not in general use, no attempt can be made to list clear-cut indications. Our reasons for recommending lobectomy and pneumonectomy at the present time undoubtedly will be modified by further experience. In the present report, six cases of planned pulmonary resection in tuberculosis are summarized (three lobectomies and three pneumonectomies).

From this experience and that of others, particularly of Jones and Dolley, some attempt will be made further to crystallize our present attitude about the indications and contraindications for lobectomy and pneumonectomy in patients with phthisis. Operation upon two of the six cases was performed by Dr. John Alexander, and their inclusion in this series is with his permission. Detailed reports of these two cases will be published subsequently by him.

* Read before the Section on Thoracic Surgery, Third Congress of the Pan-Pacific Surgical Association, at Honolulu, T H, September 15-22, 1939. Submitted for publication March 2, 1940.

Case 1—L C, white, female, age 32 On August 3, 1936, a total left pneumonectomy was performed at the University of Michigan Hospital by Dr John Alexander, assisted by the author This patient had an atelectasis of the left lung and an advanced fibrostenosis of the left stem bronchus She was seriously ill because of obstruction of secretions Thoracoplasty seemed inadvisable because of the marked bronchial obstruction Dilatation of the stricture was impossible After a prolonged convalescence she eventually became well and to-day is leading practically a normal life

It is interesting that this is one of the first planned pneumonectomies in tuberculosis of which we have record

Case 2—A O's, white, female, single, age 33, was referred by Dr Robert Peers, of Colfax, Calif A total right pneumonectomy was performed by Dr Emile Holman and the writer at the Stanford Hospital, San Francisco, June 5, 1937 Symptoms of right-sided pulmonary tuberculosis developed in October, 1932 Bed rest alone, later supplemented

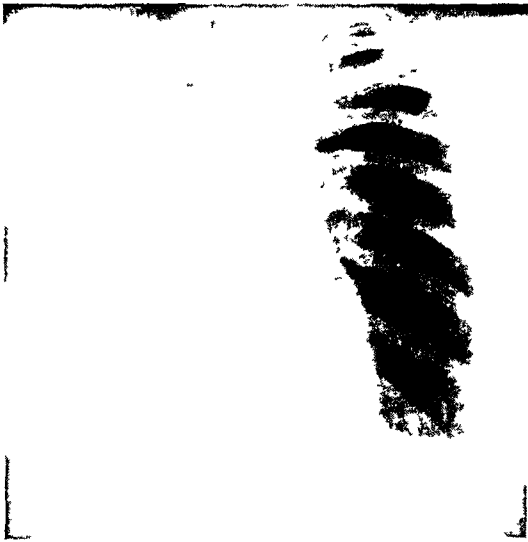


FIG 1—Case 2 Postero-anterior roentgenogram prior to thoracoplasty The base is atelectatic Questionable areas of cavitation at the level of the fifth and sixth ribs posteriorly



FIG 2—Case 2 Roentgenogram with Potter Bucky technic following ten rib thoracoplasty The right lung is completely collapsed Patient symptomatically unimproved

by induced pneumothorax for one and one-half years, resulted in slow improvement During this time she suffered from "asthmatic attacks" The sputum became negative for tubercle bacilli although she still coughed and raised purulent sputum Her "attacks" were characterized by cessation of sputum for two or three days, fever, and an irritative nonproductive cough On about the third day, sputum would be produced in large quantities and the temperature would fall These attacks often occurred at the time of menstruation A phrenicectomy effected little change in her condition Roentgenograms showed some suggestion of cavitation in the upper lobe (Fig 1) Late in 1936, a two-stage, ten-rib thoracoplasty was performed by Doctor Holman There were no visible uncollapsed cavities following thoracoplasty (Fig 2) The sputum was decreased in amount but the patient still expectorated from 25 to 50 cc The harassing cough remained unchanged

Between the stages of her thoracoplasty, stenosis of the right stem bronchus was demonstrated bronchoscopically Following the second stage, bronchoscopy again was performed on two occasions (P C S) The right stem bronchus was so narrowed that only a dimple remained Successful dilatation was not possible

Indications for Pneumonectomy—The patient had a persisting chronic infection and

a highly obstructed stem bronchus. Presumably the tuberculosis was arrested since tubercle bacilli were not found in the sputum. The patient's cough was worse following thoracoplasty. It was obvious that the lung was totally atelectatic and that the patient's illness continued because of the lack of drainage of infectious secretions. Pneumonectomy, therefore, was recommended.

Operative Procedure and Subsequent Course—The right lung was exposed through a posterior incision after regenerated ribs had been removed. The visceral and parietal pleurae were densely adherent. Eventually the hilum was mobilized and a Carr automatic hilar ligature applied. The lung was amputated and the wound closed in layers. Closed intercostal drainage was established. The immediate postoperative convalescence was stormy and bronchopneumonia developed at the left base. Later the wound was opened and packed. Eventually it closed completely by granulation. Clinically, bronchial fistula was never a problem. She has led an essentially normal existence although there has been moderate dyspnea, probably as a result of a slight narrowing of the lower trachea. Recently a few tubercle bacilli were found in her sputum. Bronchoscopic examination revealed a collection of thick pus in the shallow stump of the right stem bronchus. It is possible that a tortuous bronchial tract may persist leading to a focus in the collapsed interpleural space. The left lung remains clear.

Pathologic Examination—Dr. James B. McNaught, Stanford Department of Pathology. The lung was shrunken, firm, and entirely atelectatic. Scattered bronchiectases were present. Microscopically, fibrous tissue replaced the alveolar structure. The bronchiectasis was nontuberculous. Most of the tuberculosis appeared quiescent. It was characterized by caseous necrosis with beginning calcification. Only occasional giant cells were seen. Of importance was the fact that the most highly cellular tubercles were located predominantly in the submucosa of the medium and larger bronchi.

Case 3—A. H., white, female, age 27. Referred by Dr. Elliott T. Smart of Bret Harte Sanatorium. A total left pneumonectomy was performed, October 4, 1938, by the author. Roentgenographically, the original tuberculosis consisted of a minimal lesion in the left lower lobe (Fig. 3). Cough and sputum were out of proportion to the amount of tuberculosis. The sputum was positive for acid-fast bacilli and the patient had a constant wheeze. Accordingly, she was bronchoscoped shortly after admission. Severe tuberculous ulceration and stenosis of the left lower lobe bronchus was found. This was treated with high frequency cauterization five times at monthly intervals. Ulceration almost entirely healed and fibrous stenosis increased. Wheezing disappeared. Following an upper respiratory infection three months later, wheezing again became prominent and bronchoscopy showed extension of the ulcerative lesion to the carina. Following cauterization, partial atelectasis of the left lung developed. There was subsequent clearing, followed by the development of complete atelectasis (Fig. 4). Anterior and posterior mediastinal herniation of the right lung developed. Following further cauterization, the bronchial lesion became a pure fibrous stenosis. Pneumothorax had been attempted without success. There was no change following temporary paralysis of the left phrenic nerve.

Indications for Pneumonectomy—This patient was observed for six months following the development of total atelectasis. During this time she was always moderately toxic and her sputum persistently contained tubercle bacilli. She had occasional febrile episodes. Bronchial dilatation was attempted, but the patient's symptoms did not abate. Thoracoplasty appeared futile since the lung was already collapsed. The continued toxicity from obstruction of secretions due to the advanced bronchial stenosis made total removal of the lung seem the only surgical procedure offering the patient a chance of a return to health. The patient was in relatively good condition and the opposite lung was clear.

Operative Procedure and Subsequent Course—The left lung was exposed through a posterior incision with removal of the fifth rib. Adhesions completely obliterated the pleural cavity. The hilar vessels were individually ligated and the bronchus was divided.

and closed with silk. The vessels were much smaller than normal. The thoracic cavity was closed without drainage and air was aspirated. The immediate postoperative convalescence was excellent. After the tenth day, the patient became increasingly toxic with fever, cough, and foul expectoration. Repeated aspirations of fluid from the left chest



FIG 3—Case 3. Postero-anterior roentgenogram. A minimal tuberculous lesion is seen in the left lower lobe.

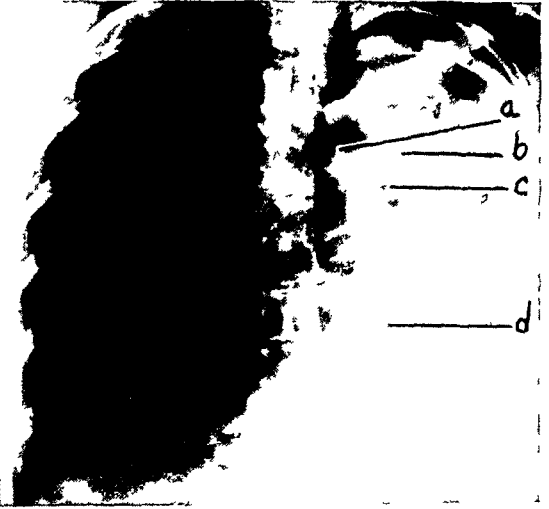


FIG 4—Case 3. Roentgenogram with Potter Bucky technic. Total atelectasis of the left lung. Multilocular cavitation at the apex. (a) Carina. (b) Anterior mediastinal herniation of right lung. (c) Stenosis of left bronchus. (d) Posterior mediastinal herniation of right lung.



FIG 5—Case 3. Mediastinal aspect of atelectatic left lung. The stem bronchus is divided at its junction into upper and lower lobar branches. Considerable mucosal thickening is evident. The lower lobar bronchus is partially obstructed.

showed no evidence of infection at first. Eventually a localized empyema with bronchial fistula became evident. Rib resection was performed but a nontuberculous spill-over infection at the right base already had occurred. The patient was temporarily improved.

following drainage by rib resection. Later it was necessary to drain a rectal abscess and the patient died ten weeks following pneumonectomy.

In retrospect it was a mistake not to have drained the pleural cavity at the time pneumonectomy was performed.

Pathologic Examination—The left lung measured 16x10x3 cm (Fig 5). Except for a small portion of the lingula, it was entirely airless. Sections through the main lower lobe bronchus and its branches showed progressively increasing obstruction distally. The mucosa was diffusely ulcerated and the lumina filled with caseous material (Fig 6). On cut-section, the lower lobe (site of the original lesion) showed fibrous, patchy infiltration and one small cavity filled with caseous debris. In the upper lobe were soft, conglomerate



FIG 6—Case 3. Photomicrograph showing the obstructed lumen of left lower lobar bronchus. Complete destruction of mucosa by tuberculous ulceration. (X200)

tubercles and several small cavities. The cut-surface was diffusely infiltrated with whitish-yellow, soft caseous material, obviously more active and of more recent origin than the lesions in the lower lobe.

COMMENT ON PNEUMONECTOMY—There is a striking similarity in the history of these three patients and in the symptoms they exhibited. The syndrome is one which we now invariably associate with progressive ulcerative bronchial disease and subtotal bronchial obstruction. In Case 3 an excellent opportunity was given to observe the progression from ulcerative tuberculous bronchial disease to subtotal fibrous obstruction. In this case, unfortunately, local treatment for the ulcerative disease was not effective in preventing the stenosis. In general, our experience leads us to believe that the chances of curing an ulcerative lesion are better with local treatment than if it is not employed. The clinical appreciation of tuberculous bronchial stenosis with its resultant pulmonary atelectasis is a relatively recent development in tuberculosis work. This knowledge in great part has followed the increasing use of the bronchoscope in patients with phthisis. Eloesser's¹³ contributions in

1931 and 1934 were of great value. The prolonged illness of patients with this type of pulmonary disease is now better understood. We are able to evaluate the varied symptoms associated with intermittent obstruction of secretions and the pathologic basis for them. In a broad sense, this type of case, which is not uncommon, refutes the belief of those who feel that pulmonary atelectasis is a favorable prognostic sign in tuberculosis. We feel, on the contrary, that most of these patients cannot become entirely and permanently well without surgery.

No one who has had the opportunity of removing one of these lungs or who has seen them at autopsy can help but be impressed with the difficulties which may follow thoracoplasty. The lungs already are collapsed to the maximum degree. In fact, as illustrated in Case 2, thoracoplasty may be followed by an aggravation of the patient's symptoms, particularly the distressing cough. The pulmonary tissue is extensively carnified. Areas of diffuse pneumonitis are interspersed with small abscess cavities or patches of bronchiectasis. Often this process is predominately tuberculous in nature. As far as the patient is concerned, however, it makes little difference whether or not the tuberculosis is arrested, since nontuberculous suppuration causes continued toxicity if there is bronchial obstruction.

Case 4—T. L., Mexican, female, age 31. Referred by Dr. Elliott Smart of Bret Harte Sanatorium. A left lower lobe lobectomy was performed February 25, 1939, by the author. In 1934, this patient was admitted to the San Joaquin General Hospital with a diagnosis of tuberculous pneumonia of the left lower lobe. The sputum contained many acid-fast bacilli. Pneumothorax was instituted immediately but was discontinued after three months because ineffective. A permanent phrenic paralysis was produced. The sputum continued to be positive for acid-fast bacilli. A large cavity was consistently present in the gutter behind the heart but could be seen clearly only by means of oblique or lateral roentgenograms (Fig. 7). No tuberculosis was seen in the upper lobe. An excellent pneumoperitoneum was maintained for one year with no appreciable change in the size of the cavity (Fig. 8). The patient had been treated by various conservative means for a period of five years.

Bronchoscopy revealed a slight narrowing of the left lower lobar bronchus. Purulent secretions came from the left lower lobe. Otherwise the examination was negative.

Indications for Lobectomy—This patient's disease was sharply limited to the left lower lobe. The upper lobe was entirely free as far as physical examination and roentgenography could determine. The cavity was 4.5 cm. in diameter, old, and thick-walled. It was deep in the gutter and lay immediately in front of the posterior seventh and eighth ribs. In our experience, thoracoplasty for this type of lesion has not been effective. Local rib resection alone has been extremely unsatisfactory and the end-result in several cases has been a total thoracoplasty with the sacrifice of an entirely normal upper lobe. Lobectomy, therefore, appeared to be the most direct approach to the problem.

Operative Procedure and Subsequent Course—The pleural cavity was opened through a posterior incision in the fifth intercostal space. The lower lobe was densely adherent and extrapleural separation was necessary in the region of the cavity. The hilum was developed, a Roberts-Nelson tourniquet applied, and the lobe amputated. Air-tight rib resection drainage was employed. The postoperative convalescence was not remarkable. About four weeks after operation the drainage tube was covered by the rise of the diaphragm and open intercostal drainage was established more posteriorly for a small hilar empyema. This later became obliterated. The patient expectorates a few cubic centi-

meters of mucoid sputum, negative for acid-fast bacilli. There is no bronchopleural fistula. A cure is expected.

Pathologic Examination—The removed lobe was shrunken and congested, but not atelectatic. Scattered tubercles were present. The cavity was 5 cm. in diameter and its wall was thickened and fibrosed. There was no obvious bronchial disease.



FIG 7—Case 4. Left anterior oblique projection. The large cavity is easily seen posteriorly.



FIG 8—Case 4. Left lateral projection at the height of the pneumoperitoneum. Transthoracic intracavitary injection of lipiodol. The cavity has not been affected by the pneumoperitoneum.

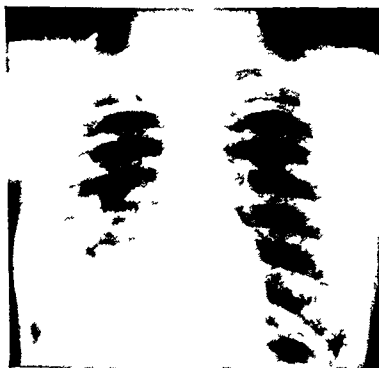


FIG 9—Case 5. Postero-anterior roentgenogram showing large tuberculous cavity in right lower lobe. Soft infiltration surrounding the cavity.



FIG 10—Case 5. Apparent closure of large right lower lobe cavity following induction of pneumothorax and pneumoperitoneum.



FIG 11—Case 5. Bronchogram in right lateral projection. There are atelectasis and bronchiectasis of the right lower and middle lobes. The cavity is not filled but lies posterior to the visualized bronchiectases.

Case 5—M. A., white, female, age 21. Referred from the Medical Chest Service of Dr. Harold Trimble at the Fairmont Hospital. A right middle and lower lobe lobectomy was performed, July 27, 1939, by the author. This patient first was admitted to the Fairmont Hospital with cavernous tuberculosis of the right lower lobe three years prior to lobectomy (Fig. 9). Shortly after admission a pneumothorax was induced. The sputum remained positive and there was roentgenographic evidence of cavity. After ten months, a pneumoperitoneum was induced. Following this procedure the cavity apparently was closed roentgenographically and the sputum promptly became persistently nega-

tive for acid-fast bacilli (Fig 10) Eighteen months later the patient developed a cold with productive cough and night sweats Roentgenograms showed that the lower and middle lobes had become atelectatic and that the cavity had reopened (Fig 11)

On readmission to the hospital, the patient presented a slight elevation of temperature, and was raising large amounts of purulent sputum with considerable difficulty The sputum was loaded with tubercle bacilli Bronchoscopy at once revealed the reason for the troublesome cough Because of atelectasis there was no air exchange in the middle and lower lobes Purulent, tenacious sputum was "puddled" in the lower lobe bronchus and filled it to beyond the level of the middle lobar orifice The mucosa was granular and superficially ulcerated Curettage specimens showed that the bronchitis was not tuber-

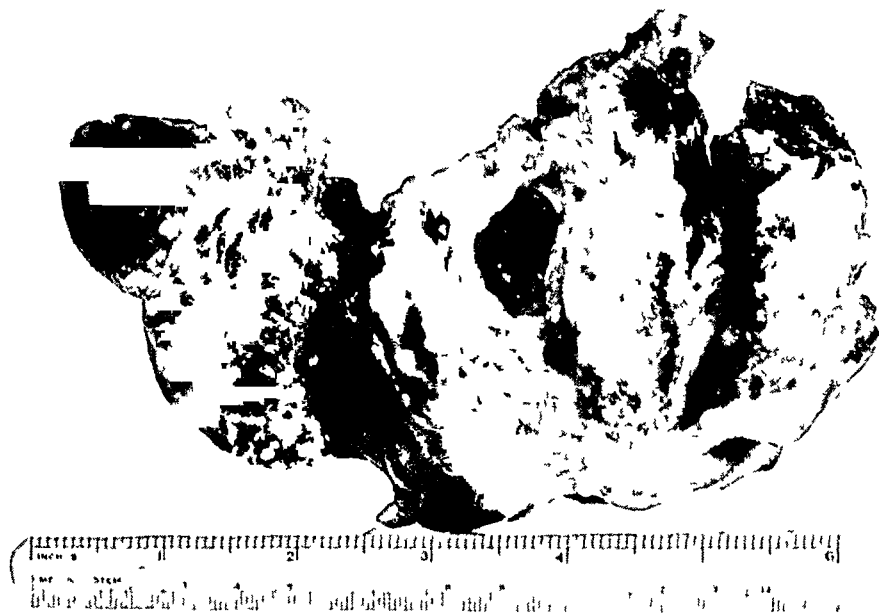


FIG 12—Case 5 Cut section through middle and lower lobes The middle lobe is on the left and shows multiple conglomerate tubercles The lower lobe is indurated and atelectatic At its center can be seen a stiff walled cavity, measuring 4.5 cm in diameter At the time of section, the cavity was completely filled with purulent and caseous material

culous in origin but undoubtedly was due to the irritation of being constantly bathed by purulent secretions Following repeated bronchoscopies and the institution of postural drainage, cough and sputum diminished and the fever subsided The mucosa became relatively normal in appearance The sputum remained persistently positive for tubercle bacilli and there was no change in the roentgenologic appearance of the lung

Indications for Lobectomy—After a period of quiescence, this patient developed an exacerbation of her old infection and atelectasis of the right lower and middle lobes occurred The large cavity reopened There was no improvement with continuation of conservative measures (pneumothorax and pneumoperitoneum) Because of the position of the diseased lobes and because of the obvious atelectasis and bronchiectasis, it was inconceivable that any type of thoracoplasty would be effective Lobectomy, therefore, appeared to be the only solution The pneumothorax was abandoned and the lung was expanded with this operation in mind

Operative Procedure and Subsequent Course—The pleura was entered through a posterior incision in the fifth intercostal space There were firm adhesions surrounding the shrunken, hard, atelectatic middle and lower lobes There were only a few adhesions

over the upper lobe and there was slight collapse of this lobe during the operation. The middle and lower lobes were amputated following mass ligation of the hilum. The wound was closed in layers and air-tight intercostal drainage employed. The immediate postoperative condition was good. Following transfusion on two occasions, however, she developed severe reactions, became jaundiced, and secreted smoky urine. Death occurred one week postoperatively. A limited postmortem examination showed the right pleural cavity to be dry. The upper lobe was almost completely expanded. There was a slight pleural reaction with early infection. There were scattered old tubercles in the upper lobe and in the left lung. The liver and kidneys were extremely friable, congested, and the site of parenchymatous degeneration. The kidney tubules were clogged with hemolyzed red blood cells. There seemed to be little question but that death was directly due to the transfusion reactions.

Pathologic Examination—The resected lobes were shrunk and entirely atelectatic (Fig. 12). There were no obvious tubercles in the main bronchi. The middle lobe was soft and flattened and measured 8.4 x 1.5 cm. The cut-surface was covered with caseous tubercles varying in size from 1 to 5 mm. The lower lobe was roughly triangular in shape and was greatly indurated. It measured 10.6 x 5 cm. On cut-section, the center of the lobe was occupied by a large irregular cavity 4.5 cm in diameter. The walls were thick and the cavity entirely filled with tenacious, purulent and caseous material.

Microscopic examination showed extensive fibrosis, atelectasis, and active caseous tuberculosis. A few submucosal tubercles were present in the main lobar bronchi but these appeared to be of no immediate significance.

Examination of the specimen confirmed our preoperative belief that any type of thoracoplasty would have been entirely ineffectual.

Case 6—P. B., white, female, age 29. A one-stage right middle lobe lobectomy was performed by Dr. John Alexander, July 7, 1939. The tuberculosis was localized to the middle lobe which was entirely occupied by a solid, fibrocalcereous lesion surrounding a cavity. It was believed that even a total thoracoplasty, including all the anterior ribs and cartilages, might not close the cavity in the cardiohepatic angle. This patient's convalescence was entirely satisfactory.

COMMENT ON LOBECTOMY—Indications for lobectomy have differed somewhat from indications for pneumonectomy. In the above cases of lobectomy, stenosis of the lobar bronchus was not a factor. The position of the cavity, however, was important. If the lesions encountered had been in an upper lobe, thoracoplasty undoubtedly would have been performed. The position of these cavities in the lower and middle lobes, together with the associated changes in the pulmonary tissue, made the effectiveness of thoracoplasty doubtful.

Pulmonary resection carries a greater risk than thoracoplasty and cannot be considered as a substitute for it. There are cases, however, in which thoracoplasty obviously is not suitable, others in which it has been performed without cure. Within this restricted group it is apparent that selected cases may be found which can be considered for some type of pulmonary resection. The tuberculosis should be fairly sharply limited to the portion of lung to be resected.

Both lobectomy and pneumonectomy may be considered either as primary or as secondary procedures. In the latter group are those cases of pulmonary resection designed to remove cavity-bearing pulmonary tissue which was not collapsed by a technically adequate thoracoplasty. Cases of this kind are occasionally seen. We doubt the advisability of removing a lobe in which a cavity

has been uncollapsed by a pneumothorax which cannot be completely abandoned, without first obliterating the interpleural space by thoracoplasty

All cases of planned pulmonary resection which are not preceded by thoracoplasty may be listed as primary procedures. Patients with total atelectasis of one lung and advanced fibrous stenosis of the stem bronchus occasionally suffer from obstructive symptoms, such as intermittent fever and harassing cough, which cannot be relieved by bouginage of the stricture. Pneumonectomy should be considered for such patients, *whether or not* their tuberculosis is apparently arrested. In patients whose bronchial obstruction is due primarily to extensive ulcerative disease, the writer feels that pneumonectomy probably should be deferred until mucosal healing and fibrostenosis have occurred. As with major collapse procedures it would seem futile to perform a pneumonectomy when faced with progressive tracheobronchial ulceration. As an indication for primary lobectomy the location of a large, isolated cavity in a lower or middle lobe is of first importance. The decision is strengthened by the presence of concomitant atelectasis and bronchiectasis, or by the discovery of a stenotic lobal bronchus. Obviously, pneumothorax, phrenic paralysis, and pneumoperitoneum, or a combination of these procedures, will have been tried prior to considering lobectomy.

A further indication is illustrated and discussed by Jones and Dolley, namely, the occurrence of repeated severe hemorrhages from a tuberculous cavity. They feel in these circumstances that lobectomy is safer than thoracoplasty. This view was questioned by Coryllos,¹⁴ and by Janes.¹⁵ The author has had no experience with this possible indication for lobectomy. In certain patients lobectomy certainly should be considered, particularly if the hemorrhage occurs in a tension cavity of the check-valve type.

SUMMARY AND CONCLUSIONS

Six cases of planned pulmonary resection for tuberculosis have been presented. These consist of three lobectomies (one bilobar) and three pneumonectomies. Two patients died following operation, one as the direct result of a transfusion reaction. Two patients are convalescing and there is every expectation of a cure. Two are leading relatively normal lives. Thoracoplasty had been performed unsuccessfully on one patient. In the other five patients, pulmonary resection was preferred as the primary procedure.

We have emphasized that resection is not a substitute for thoracoplasty. Cases occasionally are encountered, however, in which thoracoplasty seems to offer the patient little chance of becoming cured. We believe that under certain circumstances, lobectomy and pneumonectomy may be indicated in the surgery of pulmonary tuberculosis. We have presented our present conception of these indications.

The operative hazards have been discussed.

The author is indebted to Dr. John Alexander, of the University of Michigan Medical School, and to Dr. Emile Holman, of the Stanford University School of Medicine, for

their helpful suggestions and for their permission to include cases in which each was senior surgeon

REFERENCES

- ¹ Block Verhandl d deutsch Gesellsch f Chir , 77, 1882
- Ruggi, G La Tecnica della Pneumectomia nell'uomo Bologna, 1885
- ² Tuffier, T Chirurgie du poumon, en particulier dans les cavernes tuberculeuses et la gangrene pulmonaire Paris, Masson et Cie, 1897
- ³ Freedlander, S O Lobectomy in Pulmonary Tuberculosis Jour Thor Surg , 5, 132, 1935
- ⁴ Jones, J C , and Dolley, F S Lobectomy and Pneumonectomy in Pulmonary Tuberculosis Jour Thor Surg , 8, 351, 1939
- ⁵ Beye, H L Discussion, Freedlander ³
- ⁶ Eloesser, L *Ibid*
- ⁷ O'Brien, E J *Ibid*
- ⁸ Brunn, H Reported by Shipman, S , Discussion, Jones, J C , and Dolley, F S ⁵
- ⁹ Rienhoff, W F , Jr Surgical Technique of Total Pneumonectomy Arch Surg , 32, 218, 1936
- ¹⁰ Lindskog, G E Total Pneumonectomy in Pulmonary Tuberculosis Jour Thor Surg , 7, 102, 1937
- ¹¹ Crafoord, C On the Technique of Pneumonectomy in Man Stockholm, Tryckeri Aktebolaget Thule, 1938
- ¹² Eloesser, L Bronchial Stenosis Jour Thor Surg , 1, 194, 270, 373, 485, 1931-1932
Idem Bronchial Stenosis in Pulmonary Tuberculosis Am Rev Tuberc , 30, 123, 1934
- ¹³ Coryllos, P Discussion, Jones, J C , and Dolley, F S ⁵
- ¹⁴ Janes, R *Ibid*

INJECTIONS OF AIR AND OF CARBON DIOXIDE INTO A PULMONARY VEIN*

R M MOORE, M D AND C W BRASELTON, JR,† M D
GALVESTON, TEX

FROM THE LABORATORY OF EXPERIMENTAL SURGERY, UNIVERSITY OF TEXAS SCHOOL OF MEDICINE, GALVESTON, TEX

It has been repeatedly demonstrated that the injection of air into a systemic vein leads to embolism of the smaller vessels in the lung and that such embolism is not apt to be harmful unless an extremely large volume of air is injected. When air is permitted to enter a pulmonary vein, on the contrary, relatively small amounts may cause death, since the air passes directly through the left heart to the systemic arteries. In this respect, the likelihood of cerebral or medullary embolism has received particular attention. Some chance observations in the laboratory, however, suggested to us that coronary embolism is the chief danger. Consequently, in a series of animals, we have injected air into a pulmonary vein in order to study the manner of death. Furthermore, as a companion study, we have compared the effects of air with those of carbon dioxide, with the possibility in mind that the latter gas might be relatively harmless in view of its solubility and of its property of entering into chemical combination in the blood.

Method—The experiments were performed upon cats of varying size and age anesthetized by the intraperitoneal injection of sodium amytal. Artificial respiration was maintained through a tracheal cannula. The right and left fifth ribs were removed, the sternum was cut across, and the pericardium opened widely, so that the heart and lungs were clearly in view throughout the experiment. The air or other gas was injected directly into a pulmonary vein by means of an ordinary syringe and needle, a coating of oil preventing any escape of air about the plunger of the syringe. The speed of injection was limited only by the caliber of the needle, the injection requiring from one to six seconds depending upon the volume of air injected. Although most of the injections were made by way of the left superior vein, each of the other pulmonary veins was utilized at times without apparent variation in the result.

Cause of Death—In each of 30 animals death was finally caused by injecting air into a pulmonary vein. In every instance it appeared that the death resulted from obstruction of the coronary arteries. After the air was injected into the vein, within a second or two one saw air bubbles descending the coronary arterial branches on the surface of the heart‡. When the dose

* Submitted for publication July 5, 1939

† Recipient of the Dr J B Kass, Research Scholarship in Preventive Medicine

‡ The uppermost part of the left auricle, *i e*, the auricular appendage, often served as an air-trap. After injection of a small dose of air it was sometimes necessary to express the air from this site before it would pass into the left ventricle and make its appearance in the coronary arteries.

was small, only a few tiny vessels near the apex became obstructed, they remained readily visible as branching white lines until solution or absorption of the air. This required from 5 to 20 minutes depending upon the amount of air which had lodged. When only a few such branches were obstructed, there was no visible disturbance of the beat or of the function of the heart.

With larger doses the air filled both coronary arterial trees, even including the main stems.* There it remained. At times a segment of blood interposed in the column of air would be seen to oscillate slightly with the beat of the heart, but there was never any progression of the column to suggest an escape through the capillaries. This complete obstruction of the coronary arteries led to a rapid ischemic failure of the ventricles. They became pale and dilated within two or three minutes. Various degrees of block were followed by ventricular fibrillation and death with the heart in extreme dilatation. This required five or six minutes after the injection. By this time the wink reflex was lost. The animal made violent agonal respiratory movements. A minute or so later the pupils had become extremely dilated and the animal appeared dead although the aortic maintained a regular beat for some minutes longer.

The manner of death, *i.e.*, the behavior of the heart, the appearance of the animal, and the time elements which pertained, were the same as when both coronary arteries are ligated (Moore and Greenberg,⁶ 1937, Dennis and Moore,² 1938). This fact, together with the absence of convulsions and the occurrence of spontaneous agonal respiratory movements, led to the conclusion that death resulted primarily from coronary obstruction and not from embolism of medullary or cerebral vessels. The terminal cerebral asphyxia evidenced by the loss of reflexes, the dilatation of the pupils, and the agonal respirations was secondary to the failure of the heart.

In 29 of the 30 animals, death followed this cardiac pattern. There was no convulsion. In two of the animals, it was noted that the wink reflex was lost in one eye a minute sooner than in the other, however, in these

* In two animals injections of moderate doses of air repeatedly filled the right coronary artery while causing no embolism of the left artery. In two other animals the tendency was for the anterior descending branch of the left artery to become filled while the circumflex branch of the left artery and the right arterial tree received no air. In young animals with good arterial anastomoses the preservation of two of these three main arterial channels to the myocardium permitted the animal to survive. In spite of irregularities of rhythm and periods of partial dilatation of one ventricle the heart maintained its function. The disappearance of the air from the one vessel it filled required about 20 minutes. In the case of the right artery the air remained visible longest in a circular area about 1 cm. in diameter situated on the anterior surface of the heart just to the right of the interventricular sulcus and about one-third way up from the inferior cardiac border. In the case of the anterior descending artery the air tended to remain longest in a similar area on the right inferior aspect of the cardiac apex just to the left of the anastomotic connection between this vessel and the posterior descending ramus of the right coronary artery. Such areas were visible not only because the air-filled vessels appeared as branching white lines but also because the myocardium was dry, pale and gray in contrast to the moist, red appearance of the adjacent heart muscle.

animals there occurred spontaneous respiratory movements after the heart had ceased all coordinate activity, indicating that until that time the medullary centers were not paralyzed. Consequently, we are skeptical of the dangers of cerebral embolism while the horizontal position is maintained.

That the passage of air to the coronary arteries was independent of the animal's position was shown by Experiment 27, the one instance in which a convulsion did occur. In this experiment a sublethal dose of air was repeated—first with the animal board tilted to 30° head-down, then with the board tilted 30° head-up, and, finally, with the board horizontal. In the three positions there occurred apparently identical amounts of coronary embolism, the air requiring in each instance about 15 minutes for absorption. Next the animal was given a lethal dose of air with the board horizontal, and, as it was dying with the ventricles fibrillating, convulsions occurred in the hind legs. We suppose these convulsions signified cerebral embolism although they occurred 34 minutes after the injection made with the head elevated. In three of the other experiments, injections were made with the animal board inverted so that the animal was suspended in a quadrupedal walking position. Death occurred from coronary obstruction just as when the animal was lying upon its back.

We do not infer that regardless of position all air injected by way of a pulmonary vein passes into the coronary arteries, but rather that, being the first aortic branches, the coronaries receive a considerable proportion of the air. In every animal we studied the coronary embolism of itself caused death, leading as it did to ventricular fibrillation.

Fatal Dose of Air—Ordinarily, injections of volumes up to $\frac{1}{4}$ cc per pound body weight were tolerated without sufficient disturbance of the heart to harm the animal. This dose would amount to 37.5 cc of air into a pulmonary vein of a man of 150 lbs.* Doses exceeding $\frac{1}{4}$ cc per lb were apt to be fatal and doses exceeding $\frac{1}{2}$ cc per lb were regularly fatal.

Effects of Carbon Dioxide—In a number of animals we injected pure carbon dioxide into a pulmonary vein†. It appeared to be harmless. We made repeated injections, some as large as 3.0 cc per lb body weight, a quantity

* In six cats, we determined the ratio of heart weight to body weight. The figure ranged from 0.31 per cent to 0.55 per cent with an arithmetical average of 0.39 per cent. Smith⁸ (1928) found that in man the normal heart averaged 0.43 per cent of body weight in the male and 0.40 per cent in the female.

† Samples were taken from a number of tanks of commercial carbon dioxide purporting to be pure. In every instance chemical analysis proved air to be present and injection of such a sample into a pulmonary vein resulted in coronary embolism in proportion to the amount of air in the mixture. Thereafter, we generated our own carbon dioxide by pouring concentrated hydrochloric acid over marble chips in a small glass flask. After the first violent bubbling had ceased the flask was closed with a one-hole rubber stopper carrying a glass tube. This tube was fitted with a rubber connection of $\frac{1}{8}$ size to fit the nozzle of a Luer syringe. After a few minutes to permit all air to be displaced from the flask and tubing, the syringe was attached and the carbon dioxide allowed to flow into it by virtue of its own pressure, the plunger of the syringe being sealed with oil. With these precautions it was possible to obtain carbon dioxide practically free of air.

corresponding to 450 cc for a 150 lb man. In one animal we injected a dose of 20 cc per lb body weight three times in four minutes for a total dose of 60 cc per lb. No lasting embolism resulted. Thirty minutes later the same animal suffered the typical coronary embolism death from an injection of one-sixth this volume of air.

During the injection of the carbon dioxide there was a loud "slap-slap-slap" sound—the "mill-wheel" murmur. The gas was seen to fill both coronary trees within a few seconds but in 15 to 20 seconds it was entirely replaced with blood. Even the tremendous doses employed caused too short a period of coronary obstruction to disturb the heart's rhythm. Although immediately after the injection the vessels were filled, within a few seconds a column of blood could be seen advancing down each artery. With every systole of the heart this column of blood advanced several millimeters. In eight or ten beats of the heart only a little of the gas remained visible. This remainder vanished in another few seconds except in instances when the gas was contaminated with air, in which cases a varying number of the smaller arterial branches remained visibly obstructed for some minutes.

Discussion—In considering the dangers attending the entrance of air into the circulation one must distinguish between the systemic and the pulmonary veins. The fear that the accidental entrance of air into a systemic vein may result in sudden death has been dispelled to a great degree by the repeated demonstration that large volumes of air can be injected into the veins of animals without fatal results. In the dog from 3.5 cc (Harkins and Harmon,¹ 1934) to 70 cc (Wolffe and Robertson,¹¹ 1935) per lb body weight is required to kill when given into the femoral vein in a single injection. Richardson, Coles and Hall⁷ (1937) tried a method of continuous injection at a slow rate and in one dog injected 3,910 cc over 87 hours' time before death occurred. Similar experimental results can be found as far back in the medical literature as one cares to go. In 1889, in a demonstration before the Philadelphia County Medical Society, Dr H. A. Hare injected 60 cc of air into the jugular vein of a 12-pound dog without harmful effect. In describing his experiments, Hare³ wrote "Magendie states that he has thrown, with all the force and celerity of which he was capable, 40 or 50 pints of air into the veins of a very old horse without his dying immediately, and Cormack (1837) blew the contents of his chest, twice filled, into the jugular vein of a horse before the animal exhibited any signs of uneasiness. Barthelmy has also found that in six horses, weakened greatly by the withdrawal of blood, as much as four to six liters of air must be introduced intravenously to cause death, and estimates, in consequence, that a man weighing 136 lbs would be killed only by two-thirds of a liter." Hare concluded that "enormous amounts of air must enter a vein to cause death," and that "no such quantity can possibly find its way into a vein which has been injured with the knife of the surgeon."

Numerous studies have shown that air which enters a systemic vein is churned with the blood in the right ventricle to form a froth. Because of its compressibility this froth interferes to some extent with the expulsion of blood

from the ventricle. This phase, which is accompanied by a loud murmur, lasts but a few moments. The froth is ejected into the pulmonary artery and the bubbles of air lodge in the smaller vessels of the lung. Nitrogen is so sparingly soluble that the vessels remain obstructed for many minutes. Although massive doses of air may cause death in this manner, the pulmonary vascular bed is so capacious that large amounts are tolerated without sufficiently widespread obstruction to bring the lesser circulation to a stop. Furthermore, the pulmonary vessels are such an effective barrier that ordinarily none of the bubbles reach the left heart to lodge as emboli in the coronary or cerebral circulations.

In the case of a pulmonary vein, however, there is no capillary barrier to prevent the air reaching the left heart. As a result, small quantities, by lodging in certain medullary or coronary vessels, may cause cessation of respiration or failure of the heart. Van Allen, Hrdina and Clark⁹ (1929) found that the dog's maximum tolerance for air injected into a pulmonary vein was only 15 cc per Kg body weight, whereas one dog survived an injection into the jugular vein of 76 cc per Kg. In the experiments we have reported, the maximum by way of a pulmonary vein for the cat was 11 cc per Kg. Van Allen, Hrdina and Clark stressed the principle of "air buoyancy." Because of the gravity factor the air tends to pass to the uppermost vessels. These workers found that with the animal in the dorsal, recumbent, horizontal posture the arch of the aorta is high and serves as a trap, as a result of which much of the air passes out the great arch branches to the head, neck, and upper extremities. With the head down little of the air passes to the fore part of the body but the coronary vessels are heavily involved.

In our experiments with cats little evidence of harmful cerebral embolism was encountered. On the contrary, regardless of the position of the animal, a fatal coronary embolism was the rule. Considering the position and configuration of the aortic sinuses it would be our judgment that the ventral recumbent position with the head down might result in the air passing by the coronary orifices without entering them. Except in occasional operations, however, this position would be impracticable. Moreover, in view of our experiments, we feel that there is little hope of lessening the dangers of air embolism by placing the patient in any special position.

To compare oxygen embolism with air embolism, Harkins and Harmon⁴ (1934) calculated from the oxygen-unsaturation of venous blood that the minimum fatal dose of oxygen would be approximately 10 per cent greater than the minimum fatal dose of air. In a few animals in which we injected oxygen taken from commercial tanks which were labelled "pure," the gas appeared to produce just as lasting embolism as did air.

In this respect, the contrast between carbon dioxide and either air or oxygen was striking. Pure carbonic acid gas would not produce a lasting embolus. In explaining this difference one should bear in mind that carbon dioxide is an extremely soluble and highly reactive substance. We suppose that its solubility and its capacity as a weak acid to unite with the alkaline blood

buffers are the chief factors accounting for the rapid disappearance of gaseous carbon dioxide from the vessels. We do not believe that the gas escaped through the capillaries into the venules, for we never saw bubbles ascending the coronary veins. Furthermore, if one watched large bubbles of carbon dioxide gas in the middle of a column of blood, he saw them suddenly vanish as though they had dissolved in the blood.

The finding that pure carbon dioxide gas does not produce stable emboli when it is introduced into a vein, suggests several practical applications. It might well be substituted for air to provide the desired degree of collapse during closed intrapleural operations such as, for example, the endoscopic severing of pleural adhesions. While its absorption would probably be too rapid for use in therapeutic pneumothorax, it should be a very safe substance for the exploratory initial fill in a patient in whom pneumothorax is desired. Although the fact that carbon dioxide is much heavier than air suggests that it could be used in open thoracotomy, any admixture of the gas with air would lessen the protection from embolism. The authors have injected large amounts of carbon dioxide into the pleural cavity of the cat and know that the gas has been used without harm for pneumoperitoneum. However, since we have not injected it into the pleural cavity of man, we can make no recommendations in this regard other than to emphasize the necessity for the carbon dioxide to be pure if all effects are to be avoided.

We have been able to find only one previous report of the injection of carbon dioxide into veins. In 1924, Colle¹ reported that it produced embolism just as did air. We suspect that he was led astray through the use of ordinary commercial carbon dioxide, which, as we have noted, is often heavily contaminated with air.

In conclusion, it might be stated that the embolic effect of air requires an explanation. If blood passes through the smaller vessels, why cannot air? Apparently the lodging of air in the vessels centers about the fact that the air is present in bubbles having a resistant liquid film. Wilson and Ries¹⁰ (1923) showed that with certain colloidal solutions the surface films of the foam behave as gel-like plastic solids rather than viscous liquids. As a result the superficial viscosity may be more than 1,000 times that of water. Such bubbles are extremely resistant to rupture. Similarly, Langmuir⁵ (1938) has emphasized the viscosity and elasticity of certain protein films on water and believes that in such films the protein molecules actually undergo a form of "denaturation" to form a homogenous, continuous structure. It is our supposition that in air embolism the films of blood about the air bubbles have assumed to some degree this same rubber-like quality.

SUMMARY

A considerable proportion of the air injected into a pulmonary vein of the cat lodged as emboli in the coronary arteries. This occurred regardless of the animal's position. In 30 consecutive experiments, the injection of a volume of air equalling or exceeding 0.5 cc per lb body weight caused a typical

coronary death In only a few cases was there accompanying evidence of cerebral or medullary disturbance

Upon injecting pure carbon dioxide into a pulmonary vein it was found that this gas would not produce a stable coronary embolus Although an injection of 2 cc per lb body weight filled the coronary vessels, the gas was entirely taken up by the blood in 15 to 20 seconds and the heart was not visibly affected

The appearance and behavior of the heart following injections of air and of carbon dioxide are described and the mechanism of an embolism is discussed In relation to the absence of harmful effects from the intravenous injection of carbon dioxide certain practical applications are suggested

REFERENCES

- ¹ Colle, G Sugli effetti della introduzione di gas in circolo Arch ital di chir, 9, 419-454, 1924
- ² Dennis, J, and Moore, R M Potassium Changes in the Functioning Heart under Conditions of Ischemia and of Congestion Am Jour Physiol, 123, 443-447, 1938
- ³ Hare, H A The Effect of the Entrance of Air into the Circulation Therap Gazette, 13, 606-610, 1889
- ⁴ Harkins, H N, and Harmon, P H Embolism by Air and Oxygen, Comparative Studies Proc Soc Exper Biol and Med, 32, 178-179, 1934
- ⁵ Langmuir, I Cold Spring Harbor Symposia on Quantitative Biology, 6, 136-137 and 161, 1938
- ⁶ Moore, R M, and Greenberg, M M Acid Production in the Functioning Heart under Conditions of Ischemia and of Congestion Am Jour Physiol, 118, 217-224, 1937
- ⁷ Richardson, H F, Coles, B C, and Hall, D E Experimental Gas Embolism Canad Med Assn Jour, 36, 584-588, 1937
- ⁸ Smith, H L The Relation of the Weight of the Heart to the Weight of the Body and of the Weight of the Heart to Age Am Heart Jour, 4, 79-93, 1928
- ⁹ Van Allen, C M, Hrdina, L S, and Clark, J Air Embolism from the Pulmonary Vein Arch Surg, 19, 567-599, 1929
- ¹⁰ Wilson, R E, and Ries, E D Surface Films as Plastic Solids Colloid Symposium Monograph, U of Wisconsin, pp 145-173, 1923
- ¹¹ Wolfe, J B, and Robertson, H F Experimental Air Embolism Ann Int Med, 9, 162, 1935

CONSERVATIVE ELECTROSURGICAL EXCISION OF SUBESOPHAGEAL, CHRONIC PENETRATING OR ACUTELY PERFORATED GASTRIC ULCER

REPORT OF AN UNUSUAL CASE THUS TREATED—WITH GOOD END-RESULTS

REGINALD H. JACKSON, M.D.

MADISON, WIS.

FROM THE JACKSON CLINIC, MADISON, WIS.

CHRONIC, indurated, penetrating or acutely perforated gastric ulcers, situated in the subesophageal area of the stomach, present, from the standpoint of feasible surgical attack, difficult and hazardous problems. Access to the lesion may be so difficult and impractical as to preclude the possibility of a partial gastrectomy. Total or subtotal gastrectomy in comparatively young patients is repugnant except for a malignant neoplasm. Gastro-enterostomy alone offers little, the beneficial reparative changes anticipated in the ulcer, through drainage and chemical change, possibly being nullified, as suggested by Deansely,² by too great a distance from the lesion. Attempt at direct excision, or cautery destruction of the ulcer in addition to the performance of a gastro-enterostomy may, in a subesophageal lesion, be fraught with great hazard.

In 1936, Wells,¹ of Liverpool, reported four cases of chronic subesophageal gastric ulcers which he had treated, with most gratifying results, by performing an antecolic Pólya-Moynihan partial gastrectomy, the line of gastric section being made below the level of the ulcer, so that the ulcer was left in the remaining portion of the stomach.

Deansely,² of Wolverhampton, independently devised the same method of dealing with these cases and reported favorably on four. Walker,³ in reporting on six additional cases operated upon by this method, states "Of these ten cases [his own and those of Deansely], nine have been traced and eight can be regarded as cured, they are leading normal active lives, having no symptoms except a little feeling of fulness after meals." Pauchet and Luquet⁴ strongly advocate the so-called "groove resection" for ulcers in the upper third of the stomach. Where the ulcer is not too large and lies in an accessible position on the lesser curvature, this procedure would seem the preferable method, as it removes the ulcer *in toto*. Where a very large indurated gastric ulcer lies in a direct subesophageal position, as was found in one of our cases, or where an acute perforation presents, as was true in another, this procedure would not be feasible. Jejunostomy with physiologic rest of the gastric function may or may not result in cure. In the event of failure, the economic and time loss is very disappointing to the patient.

Transgastric approach, with actual cautery treatment of the ulcer and suture from within, may temporarily be satisfactory, but is prone to be fol-

lowed later by recurrence of symptoms and identification of the ulcer crater on roentgenologic study. The location and size of the ulcer in the case we are reporting was unique in our experience, and the technical procedure employed was one which, at the time, seemed to offer little promise of being more than temporarily beneficial. The unexpectedly smooth convalescence and subsequent freedom from all previous symptoms merit a report and a description of the technical procedure followed. In our opinion and experience, it



FIG 1—Roentgenogram, September 8, 1937, showing large, subesophageal gastric ulcer

offers "another way out"—a comparatively safe and easy one—for the surgeon confronted with a situation where a "gutter resection" is impracticable and a Wells partial gastrectomy, leaving the ulcer in the gastric remnant, would be a formidable and hazardous procedure.

Case Report—Clinic No 80500 T W, white, male, age 41, married, truck driver, admitted September 7, 1937. Chief Complaint Stomach trouble.

Previous History—Appendicectomy elsewhere, in 1923. For past seven years has had periodic "stomach upsets", burning epigastric distress with belching, especially when stomach was empty, sometimes relieved by food and soda.

Present Illness—For past three months these symptoms have persisted incessantly. Very often the taking of food seems to "set the stomach on fire". The epigastric pain has steadily increased in severity. There had been no improvement under a rigid ulcer

dietetic and medicinal regimen The patient had lost 25 pounds during the past four months

Physical Examination—Rather frail, sickly looking man with typical stomachic facies Head, throat, chest and extremities negative Blood pressure 105/65 Tenderness was elicited on deep pressure high in epigastrium, otherwise negative

Laboratory Data—Blood hemoglobin 80 per cent, red blood count 4,450,000, leukocytes 9,500, Wassermann negative Gastric analysis Total acid, in three-quarters of



FIG 2—A large, indurated, subesophageal gastric ulcer All organs except stomach were normal The stomach was entirely free from abnormal attachments, even over the area where the lesion was situated A malignant lesion on an ulcer base was suspected

an hour, 90, in one hour, 84, in one and one-quarter hours, 74, free hydrochloric acid, in three-quarters of an hour, 64, in one hour, 58, and in one and one-quarter hours, 48

Röntgenologic Examination—September 8, 1937 "There is a large gastric ulcer in the upper part of the upper third of the lesser curvature of the stomach" November 11, 1937 "The ulcer in the upper area of the lesser curvature previously described is confirmed and is more conspicuous than at the previous observation" (Fig 1)

Staff Consultation—May be large gastric ulcer or, judging from size of crater defect, a malignant neoplasm Exploratory celiotomy advised

Preoperative Diagnosis—Gastric ulcer or neoplasm *Postoperative Diagnosis* Large penetrating subesophageal gastric ulcer

Operation—November 16, 1937 Under spinal pontocaine anesthesia, the abdomen was opened through a long, left paramedian, epigastric incision *Operative Pathology* All organs except stomach were normal The stomach was entirely free from abnormal attachments, even over the area where the lesion was situated On first palpating the cardiac end, a large neoplasm was suspected The lumpy induration was decidedly

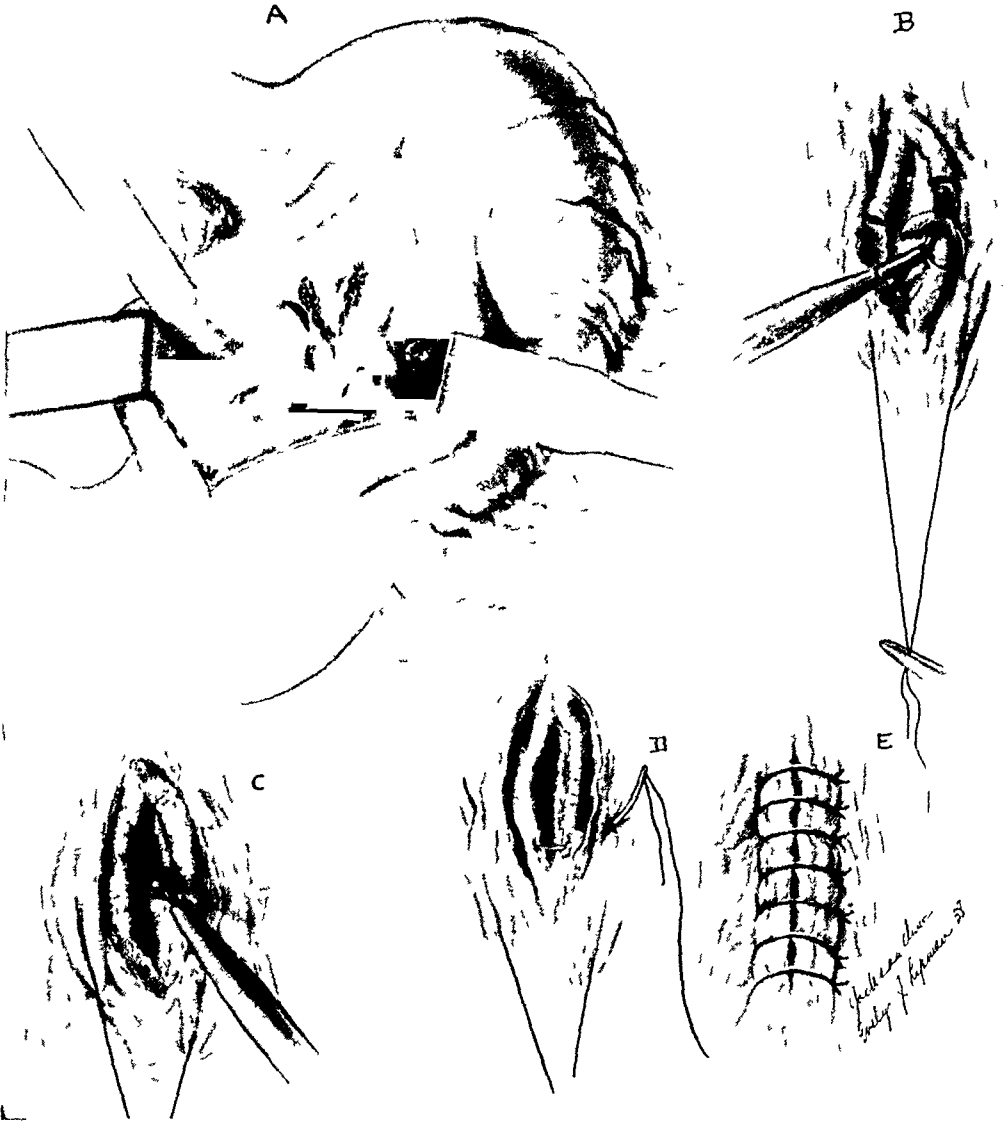


PLATE I—(A) Transgastric approach With a gooseneck Cameron light the lower end of ulcer was inspected When the stomach was quiescent the ulcer assumed an oval shape 6 cm long and 3 cm wide, when a peristaltic wave occurred it changed to a slit like form, the contracting edges firmly grasping the palpating finger

(B) With the radio loop instrument, thick shavings of crater edges were removed for microscopic examination No suspicion of carcinoma was found

(C) The base of the ulcer was sterilized with the ball pointed instrument (coagulating current)

(D) Heavy interrupted 30 day chromic gut sutures were placed, needles passing through serosa and muscular layers

(E) Appearance after all interrupted chromic gut sutures had been placed

humped-up directly below the esophageal entrance and extended down the lesser curvature for several inches, being decidedly thicker on the posterior gastric wall than on the anterior (Fig 2) A "gutter resection" was not feasible The wide extent of the massive induration excited the suspicion that a malignant degeneration had occurred in a chronic

ulcer base. If so, a total gastrectomy would be futile. It was deemed advisable to ascertain the underlying pathology by direct intragastric inspection and biopsy.

Transgastric Approach—Several heavy silk traction sutures were placed high on the anterior gastric wall and a four-inch oblique incision made (Plate I A).

The stomach, aside from the lesion, was completely flaccid and empty, continuous gastric suction having been maintained for the preceding 12 hours. With ribbon retractors holding the edges of the gastric wall far apart, it was possible, with a gooseneck Cameron light, to inspect the lower end of the crater. When the stomach was quiescent,



FIG 3—Roentgenogram of stomach one year and two months after operation. The site of the former ulcer defect is smooth.

the crater assumed a longitudinal oval shape, 6 cm long and 3 cm wide, when a peristaltic wave occurred, this changed to a slit-like form, the edges approximating each other. A finger inserted into the crater was firmly held by the contracting edges. The crater, throughout its entire length, had penetrated through the musculature of the gastric wall. Counter palpation with a finger of the other hand over the crater area revealed a well-formed, thick, plastic base protection.

A heavy silk traction suture was applied to the inside of the posterior gastric wall just proximal to the lower end of the crater. This helped materially in drawing down the crater.

With the wire loop electrode of the electrosurgical instrument several 1 cm thick shavings were removed from the crater edges and examined (Plate I B). They showed only chronic inflammatory changes with no suspicion of carcinoma. Both edges of the crater were repeatedly beveled down with the loop, using alternately the cutting and coagu-

lating currents until definite muscular tissues were exposed from end to end, and practically normal gastric mucosa fringed the edges. This assured removal of the ulcer except for its base. There was no appreciable hemorrhage from the "looping excision," small bleeding points being directly controlled with the coagulating current.

A ball-pointed electrode was then applied thoroughly over the base of the crater (coagulating current) to sterilize it (Plate I C).

The two edges were then approximated by 30 day No. 2 chromic catgut interrupted sutures, inserted 1 cm. from the edges and passing through the entire gastric wall but not penetrating the plastic base (Plate I D). The proximal sutures, after tying, were left long and served most efficiently as tractors in placing the next higher-up suture. Step by step the denuded stomach wall edges were thus approximated. The extreme upper end was quite difficult but was satisfactorily accomplished (Plate I E). Every few moments a gush of esophageal mucus flooded the upper end of the area. An examining finger detected the esophageal opening at 3 cm. above the highest suture.

After closing the gastric exploratory incision, a posterior gastro-enterostomy was performed.

Convalescence was uneventful. Continuous gastric suction was maintained for ten days. The patient was entirely free from his former symptoms immediately following the operation and has remained so up to the present time, January, 1939. The wound healed by primary intention.

Roentgenologic Report—January 12, 1938. No defect is seen in the stomach other than a gastro-enterostomy. The site of the former ulcer defect is smooth (Fig. 3).

REFERENCES

- ¹ Wells, C. Alex. High Gastric Ulcer. A Suggested Operation. *Brit. Med. Jour.*, 1, 778, May 6, 1933.
- ² Deansely. Mentioned by Walker.³
- ³ Walker, R. Milnes. The Surgical Management of High Gastric Ulcers. *Brit. Med. Jour.*, November 14, 1936.
- ⁴ Pauchet, Vidor, and Luquet, Gabriel. Surgical Treatment of Ulcers of the Superior Third of the Stomach (Groove Resection). *Surg., Gynec., and Obstet.*, 51, 367, September, 1930.

TUBERCULOSIS OF THE STOMACH

A CLINICAL AND PATHOLOGIC STUDY

RALPH C SULLIVAN, M D , NICHOLAS T FRANCONA, M D , AND
JACK D KIRSHBAUM, M D , M S

CHICAGO, ILL

FROM THE DEPARTMENT OF SURGERY AND PATHOLOGY, COOK COUNTY HOSPITAL, AND THE DEPARTMENTS OF
SURGERY, LOYOLA UNIVERSITY, AND NORTHWESTERN UNIVERSITY, CHICAGO, ILL

TUBERCULOSIS of the stomach, whether encountered as an isolated lesion, or as part of an active tuberculous process, is a very rare condition clinically or in necropsy material. It is remarkable to note the relative infrequency of gastric tuberculosis in view of the high incidence of pulmonary tuberculosis, especially when the cases show a deficient acidity and gastric secretion. One would think that the tubercle bacilli should find an ideal medium in the stomach since the latter is devoid of the usual bacteriologic protection supplied by the normal secretion of the gastric mucosa and thus rendering the organ more susceptible to the tuberculous infection. Since tuberculosis of the stomach is one of the rarest manifestations of tuberculosis in the body, it is possible that the stomach has some peculiar natural immunity to the tubercle bacilli, a protection lacking altogether in the intestinal tract.

Because of the rarity of tuberculosis isolated to the stomach, it is doubtful whether it has ever been diagnosed clinically before operation. Even during the operation, the diagnosis is usually not suspected.

As to the incidence of the disease Brodeur,¹ in 1917, found 49 authentic cases and 118 probable cases of stomach tuberculosis reported in the literature. In 1931, Good² reported three cases of stomach tuberculosis in a series of 7,416 consecutive gastric operations performed at The Mayo Clinic. Since his report, three additional cases have been reported by the Clinic. The same author, in a total of 71,871 necropsies, found that 141 cases, or about 0.2 per cent, had tuberculosis of the stomach, while necropsies of 15,165 tuberculous subjects yielded 80 cases, or 0.52 per cent.

From 1929 to 1938 (inclusive), there were 11,480 consecutive autopsies performed at the Cook County Hospital. During this period, there were 288 cases of pulmonary tuberculosis and in 242 additional cases pulmonary tuberculosis was found as an incidental finding, the patients dying of some other unrelated cause. In the former group of cases, there was *one* instance of tuberculosis of the stomach encountered, an incidence of 0.35 per cent. There was also a third group of 24 cases in which a generalized tuberculous adenopathy was the primary cause of death. In this group, one case of tuberculosis of the stomach was present. Thus, in 554 cases of tuberculosis coming to autopsy, the stomach was involved in *two* cases, while during the same

period of time, only *one* case was encountered in 75,000 surgical specimens

One may distinguish, pathologically, two types of tuberculosis of the stomach (a) Miliary tuberculosis, whereby the stomach contains single caseous tubercles located in the submucosa, or on the serosa, and is a part of the stage of generalization, and (b) ulcerative tuberculosis which is characterized by *numerous shallow, irregularly shaped ulcers* with overhanging margins and grayish-yellow bases, that rarely penetrate the muscular layer, and which may eventually cause scarring and shrinking of the stomach, simulating syphilis or carcinoma. The ulcer type is the predominating lesion, being present in 80 per cent of the cases of gastric tuberculosis reported

The sources of infection are thought to be (a) by direct invasion of the mucosa, (b) by bloodstream, (c) by the lymphatics, or (d) by direct extension

Two of our cases were of the ulcerative type, and only in one was the tuberculous process isolated to the stomach, producing clinical manifestations. Tuberculosis of the stomach is usually an incidental finding and may or may not produce clinical symptoms. In our series of four cases, only one was associated with clinical manifestations and it is this case that we are reporting in detail

Case Report—L. B., male, colored, age 34, was admitted to a medical ward, March 4, 1936, with the entrance diagnosis of carcinoma of the stomach. He stated that he had been in very good health up to six months ago when he began to notice epigastric distress that came on during, or shortly after, eating. This pain was dull and aching in character and radiated to the back, usually lasting about one and one-half hours, and was not relieved by alkalis, food intake or bowel movement. All types of food brought on the attack. He was freed completely of pain and distress only if he took no food. If pain was present it would be aggravated by walking or moving around and was not associated with nausea or vomiting. The pain had lately become more intense, lasting longer after each meal, so that patient had recently resorted to starvation. He had lost 20 pounds in six months, from 140 pounds to 120 pounds.

His past history was essentially negative. He had had no surgical operations. Other than the usual childhood diseases his past health had been good. He had had gonorrhea twice, the last attack occurring five months before, which had lasted two months. A chancre was noted two and one-half years before and it was treated with numerous "shots" in the hips and arms. Although he suffered from constipation and had to resort to laxatives he had never noticed blood or mucus in his stools. He had been married twice. He had divorced his first wife, who was living and well, and who had been pregnant twice, the first pregnancy was terminated by an induced abortion. The second lived to the age of four and one-half years. Death of this child was due to miliary tuberculosis. His second wife, living and well, had had no pregnancies. His family history was essentially negative.

Physical Examination—Temperature, 97.4° F, pulse rate 60, respirations 18. Blood pressure 96/58. He was well developed but undernourished. The pupils were equal and reacted sluggishly to light. The clavicular fossae were prominent. The examination of the lungs and heart was apparently negative. The abdomen was scaphoid in the region of the epigastrium. A small, firm mass the size of a tangerine was palpated just to the right of the midline in the epigastric region. The liver, kidneys and spleen were not palpable.

Laboratory Data—W B C, 6,850, R B C, 4,340,000, Hg, 80 per cent. Urine exam-

ination was negative. Roentgenologic examination of the stomach and duodenum showed an "annular filling defect in the pars pylorica with absence of rugae throughout the entire stomach, very suggestive of carcinoma" (Fig 1). An Ewald test meal revealed a total acidity of nine units (Topfer's method), no free hydrochloric acid, and a total gastric content of 140 cc. No blood was noted in the stomach contents or feces. A blood Wassermann test was negative.

The case was transferred to surgery as a case of carcinoma of the stomach, with syphilis to be considered.

Operation—March 11, 1936. Through an upper midline incision, the stomach and duodenum were exposed and a mass was found involving the pylorus and distal one-third of the stomach. The mass was moderately hard in consistency. The pyloric ring was

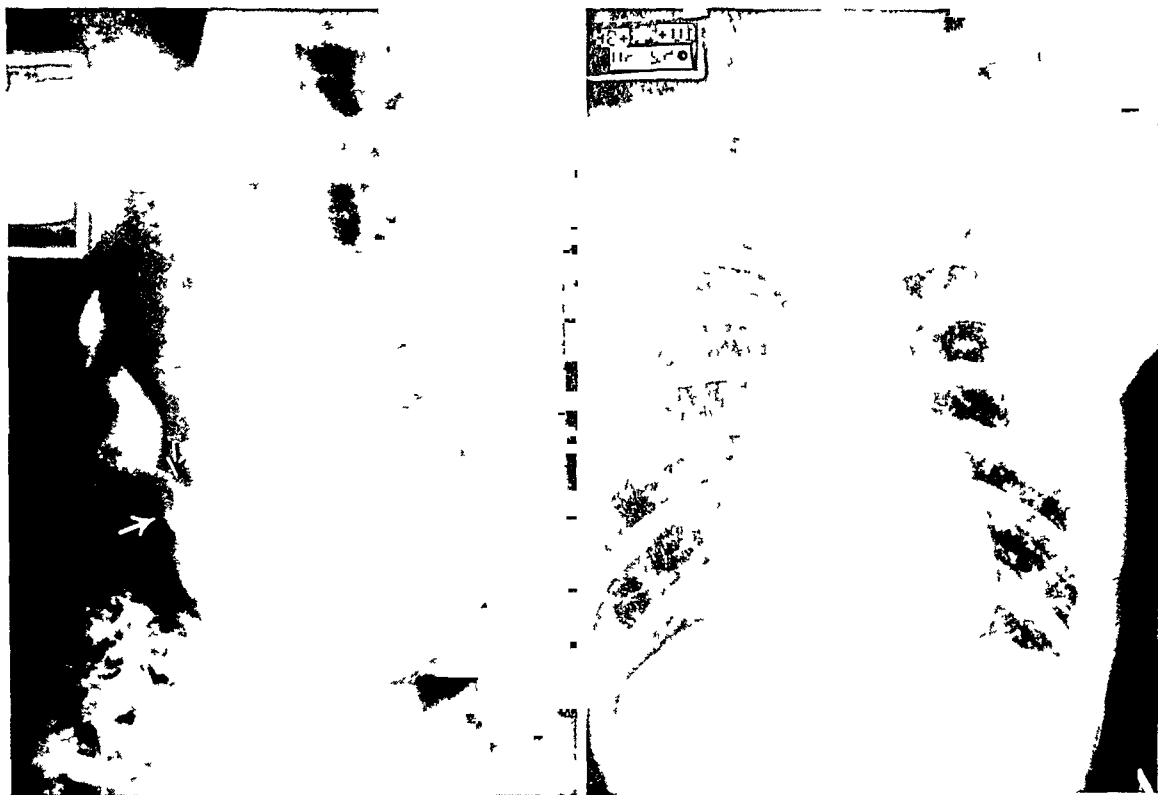


FIG 1—Roentgenogram showing involvement of the pyloric end of the stomach, with evidence of obstruction.

FIG 2—Roentgenogram of the chest, taken seven and one half months after partial resection of stomach, showing several calcified shadows in the left apex.

markedly stenosed. The lymph nodes along the lesser and greater curvatures were enlarged and prominent. Several were removed from the lesser curvature. In view of the extensive involvement of the pylorus and prepyloric region and the extent of obstruction present, a gastric resection with a posterior Polya anastomosis was performed.

The patient made an uneventful recovery except for a slight reaction following a blood transfusion of citrated blood given on the fourth postoperative day. He left the hospital on the seventeenth postoperative day, being asked to return in two to three weeks for further study, but he failed to do so and we were unable to trace him for seven months, when he returned to the hospital because of an injury to his back received by falling from the second floor while washing windows. The patient stated that he had gained 17 pounds in weight and was feeling quite well. He had to eat four to five times daily and could eat only a limited amount of food at one time.

A roentgenogram of the chest taken October 23, 1936, seven months after the operation (Fig 2) was negative except for a few small areas of calcification in the left apex. A roentgenogram of the stomach (Fig 3) revealed a well-functioning stomach. The

patient again left the hospital feeling quite well and when last seen, in December of 1938, was still gaining in weight and working at odd jobs

Pathologic Examination—Gross The tissue received was a portion of a stomach including the pylorus, and measured 13 cm in length and 10.5 cm in circumference. The wall in the region of the pylorus measured up to 12 Mm in thickness. The mucosa was deeply injected and the folds were flattened. Near the pylorus the mucosa presented a ragged, irregular defect (4.5 by 1.5 cm) and involved most of the circumference. The ulcer was shallow and the floor was smooth and discolored purplish-tan. Nearby was a second smaller defect in the mucosa, star-shaped in appearance, which measured 3.5 by 1 cm. The remaining mucosa of the stomach was smooth and light purplish-gray. The



FIG 3—Roentgenogram of the stomach, seven and one half months after partial resection, revealing a well functioning stomach

perigastric lymph nodes were enlarged, firm and measured up to 15 Mm in diameter

Microscopic—Sections taken from the stomach revealed the ulcers to extend down into the submucosa. The floor was formed by a fibrinoid necrotic tissue which rested upon a very cellular and vascular granulation tissue. The granulation tissue consisted of numerous young capillaries, swollen fibrocytes, large mononuclear cells, round cells and scattered polymorphonuclear leukocytes. The underlying submucosa was markedly thickened, fibrosed and infiltrated by accumulations of lymphocytes, occasionally perivascular and in places tending to form lymph follicles (Fig 4). In the region of the ulcer the muscularis propria was often interrupted by collections of lymphocytes, plasma cells, large mononuclear cells and single polymorphonuclear leukocytes. The muscle



FIG 4—Photomicrograph of a section through one of the ulcers in the stomach. Note the nonspecific, inflammatory changes in the floor and the wall ($\times 100$).



FIG 5—Photomicrograph of a section of the stomach showing two epithelioid cell tubercles with giant cells in the intact mucosa ($\times 150$).

bundles in places were separated by a dense fibrillar connective tissue. The serosa was also thickened by a loose connective tissue in which were accumulations of small round cells, frequently present about large blood vessels. The mucosa adjacent to the ulcers was edematous, thickened, and scattered throughout were numerous small tubercles up to the size of a high power field composed of epithelial cells, lymphocytes, and single large multinucleated giant cells of the Langerhans type (Fig 5). Occasionally the tubercles were fused together and surrounded by a dense collar of small round cells. The glands of the mucosa were frequently dilated and cystic. In the stroma, there were accumulations of polymorphonuclear leukocytes, plasma cells and mononuclear cells.

The perigastric lymph nodes contained many epithelioid cell tubercles with giant cells of the Langerhans type (Fig 6). The tubercles in some of the larger lymph nodes showed central necrosis. The sinuses were congested and the lymph follicles occasionally contained prominent germinal centers. Special stains, however, failed to reveal

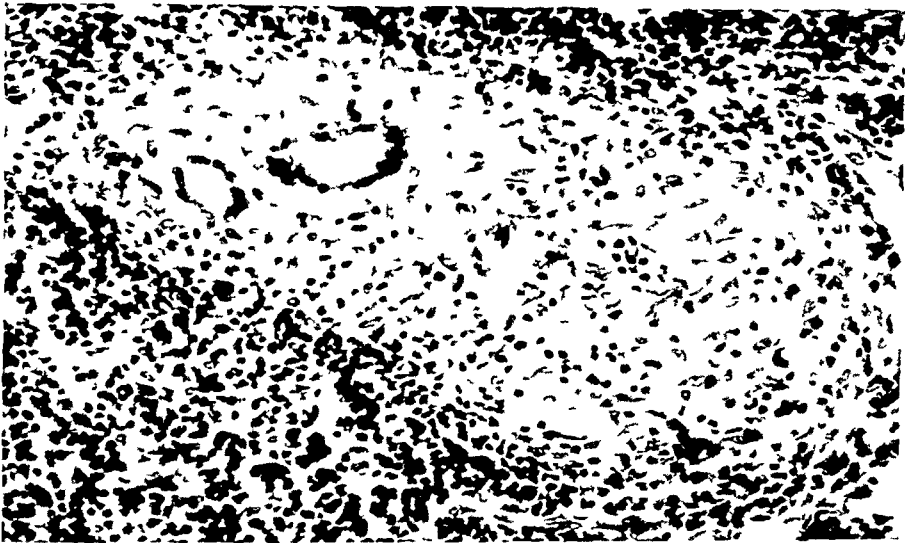


FIG 6—Photomicrograph of a section of one of the perigastric lymph nodes showing an epithelioid cell tubercle and several giant cells ($\times 300$)

the presence of tubercle bacilli. *Pathologic Diagnosis* Hyperplastic and ulcerative tuberculosis of the stomach involving the prepyloric and pyloric regions. Hypertrophic gastritis and hyperplastic tuberculosis of the perigastric lymph nodes.

Tuberculosis of the Stomach Without Clinical Manifestations—The following three cases presented tuberculous changes in the stomach which were incidental findings during autopsy.

Case 1—This case was a 38-year-old colored male, who died from an ulcerative pulmonary tuberculosis of the right upper lobe. In the stomach as well as in the ileum and cecum, there were numerous caseated tubercles that varied from pinhead to split-pea size. In the stomach the nodules were scattered along the lesser curvature of the mucosa.

Case 2—A white woman, age 33, presented a caseous tuberculous adenitis of all lymph nodes and a caseous pleuritis. There were no evidences of tuberculosis in the lungs. The stomach presented geographic-like erosions especially about the cardia and fundus. They varied from 2 to 5 cm in diameter and extended to the serosa. Over the serosa of the stomach were caseous material and loose fibrous adhesions.

Case 3—This patient was a soldier, age 39, who died during the war from a chronic ulcerative tuberculosis of both lungs, associated with an ulcerative tuberculosis of the intestines and caseous tuberculosis of both kidneys. In the stomach, on the anterior wall 5 cm below the cardia, a submucous caseous node was found which measured 16 mm in

diameter and was 6 Mm high. Histologically, the node showed an extensive caseation necrosis, well circumscribed and confined to the submucosa. (This case was seen by the late Dr. R. H. Jaffe, who was kind enough to permit us to quote.)

Discussion—Although tuberculosis of the stomach is usually seen by the pathologist at necropsy in cases of generalized tuberculosis, there remains a small number of cases in which tuberculosis manifests itself in the stomach as an isolated process. It is the latter type which is of interest to both gastro-enterologist and surgeon in view of the diagnostic problem that such a case presents. The differential diagnosis usually considered is either carcinoma or syphilis of the stomach and tuberculosis practically is never included. Even the gross examination of the excised segment of the stomach resembles a malignancy and the correct diagnosis is not suspected until microscopic examinations are made. The clinical course of tuberculosis of the stomach may resemble either a carcinoma or syphilitic process, while the roentgenologic studies favor the diagnosis of malignancy. The prognosis is usually very good following surgery in those cases in whom the general condition is often fairly good and when they have no signs of active tuberculosis elsewhere in the body. The case of Watson, Flint and Stewart³ was of extreme interest in view of the fact that the tuberculosis had produced an hour-glass deformity and microscopically a complete metaplasia in the upper fundus was observed. The latter finding is also frequently seen in the mucosa of the bronchi in cases of pulmonary tuberculosis. In Baumgartner's⁴ case, the tuberculous process in the stomach was coincidentally found with carcinoma.

Some investigators have considered the hyperplastic form of gastric tuberculosis as the primary source. This view is usually found to be incorrect, for at autopsy the primary source can often be traced to the lungs. In a series of 24 cases of gastric tuberculosis collected from the literature by Leriche and Mouriquand,⁵ only two showed evidences of clinical tuberculosis in some other organ.

Males are usually more frequently affected than females—Melchior⁶ gives the ratio of five to one, Grossman,⁷ one to three, while Broders¹ gives it as two to one. It is three to four times more common in adults than children.

Microscopically, the stomach shows superficial ulcerations and a vascular, nonspecific granulation tissue. The histologic diagnosis of tuberculosis is confirmed when tubercles are present not only in the stomach wall, but also in the regional lymph nodes. The presence of tubercle bacilli cannot always be demonstrated.

The clinical picture reveals nothing characteristic. The earliest symptoms are those of chronic gastritis with loss of appetite and a sense of fulness or pressure in the epigastrium. This is followed by epigastric distress or pain of the ulcer type, loss of weight, and vomiting. The vomiting occurs late in the course of the disease and the vomitus is dark or suggestive of gastric hemorrhage. In Becker's⁸ case, the tuberculosis was localized to the stomach.

and caused a severe gastric hemorrhage. Diarrhea, if present, is usually due to ulcerations present in the small intestines. In about one-half of the cases a mass can be palpated in the epigastrium. A majority of the cases reported have also definite evidences of tuberculosis elsewhere in the body (Gualdi,⁹ Olleros and Garcia,¹⁰ *etc*)

Laboratory data are not helpful in making a diagnosis, although the majority of cases reported reveal an absence or diminished amount of free acid. A hyperchlorhydria was found in the cases reported by Curschman¹¹ and Schlesinger.¹² Roentgenologic studies have been helpful in establishing the presence of an obstruction, but there is nothing characteristic about the nature of the defect or obstruction. In the majority of the cases reported, the roentgenologic diagnosis was carcinoma of the stomach—in others syphilis was suspected. The case of Walters, Kirklin, and Clagett¹³ offered the same diagnostic difficulties that our case did, and only after histologic studies of the excised portion of the stomach was the tuberculous nature of the lesion recognized. Biopsy of a lymph node during life may be helpful in establishing a diagnosis, as shown in the cases of Lusena,¹⁴ White,¹⁵ and Melchior,⁶ although they may be bacteriologically negative. In reviewing the reported cases, one finally comes to the conclusion that the clinical diagnosis of tuberculosis of the stomach cannot be distinguished from gastric ulcer or carcinoma, and in many respects the symptoms and pathologic findings closely resemble those of gastric syphilis.

In the treatment of tuberculosis of the stomach, a medical regimen has not proved of benefit. In a review of the surgical procedures performed, Lee¹⁶ advises resection whenever possible in the chronic cases, and gastroenterostomy in acute cases and a subsequent resection later if the patient's condition warrants it.

SUMMARY

A case of a 34-year-old colored male, with tuberculosis localized to the stomach and perigastric lymph nodes, is described. Subsequent gastric resection has thus far produced complete eradication of the disease. Epithelioid cell tubercles were present in the gastric wall and in the perigastric lymph nodes.

The clinical and pathologic features of tuberculosis of the stomach are discussed.

One case of tuberculosis of the stomach was encountered in over 75,000 routine surgical specimens, while in a series of 554 cases of tuberculosis observed in 11,480 necropsies, two cases showed tuberculosis of the stomach as an incidental finding.

REFERENCES

- ¹ Broders, A. C. Surg., Gynec., and Obstet., **25**, 490, 1917
- Good, R. W. Arch. Surg., **22**, 415, 1931
- ³ Watson, G. W., Flint, E. R., and Stewart, M. J. Brit. Jour. Surg., **24**, 333, 1936-1937
- ⁴ Baumgartner, W. Beitr. z. klin. Chir., **167**, 211-213, 1938

- ⁵ Leriche, R, and Mouriquand, E *Rev de Chir*, 39, 520, 1909
- ⁶ Melchior, E *Mitt Grenzgeb Med u Chir*, 39, 205, 1926
- ⁷ Grossman, J R *Mitt Grenzgeb Med u Chir*, 26, 771, 1913
- ⁸ Becker, F *Helvet med acta*, 4, 683-685, November, 1937
- ⁹ Gualdi, A *Gior di tisol*, p 38-39, March 31, 1936
- ¹⁰ Olleros, Rodriguez A, and de la Viesca Garcia, P *Rev españ de enferm d ap digest y de la nutricion*, 1, 745-764, October, 1935
- ¹¹ Curschman, H *Bactr z klin d Tuberk*, 2, 127, 1904
- ¹² Schlesinger, H *Munch med Wchnschr*, 61, 987, 1914
- ¹³ Walters, W, Kirklin, B R, and Clagett, O T *Proc Staff Meet, Mayo Clinic*, 11, 83-85, February 5, 1936
- ¹⁴ Lusena, G *Arch Chir*, 4, 1, 1921
- ¹⁵ White, W C *ANNALS OF SURGERY*, 105, 626, 1937
- ¹⁶ Lee, F C *Am Rev of Tuber*, 26, 323, 1932

LADD'S OPERATION FOR THE CURE OF INCOMPLETE ROTATION AND VOLVULUS OF THE SMALL INTESTINE PRODUCING DUODENAL OBSTRUCTION IN INFANCY*

ROBERT ELMAN, M D

St Louis, Mo

FROM THE DEPARTMENT OF SURGERY, WASHINGTON UNIVERSITY SCHOOL OF MEDICINE AND ST LOUIS CHILDREN'S HOSPITAL, ST LOUIS, MO

WHEN persistent vomiting in the early weeks of life yields bile stained material, a congenital obstruction in the duodenum must be considered, in this respect, at least, the lesion can be differentiated from hypertrophic stenosis at the pylorus which is associated with the return of colorless gastric contents. The type of congenital obstruction of the duodenum (*e g*, atresia, band, *etc*) is usually difficult to demonstrate at the bedside and not infrequently even at operation. The many reports in the literature of congenital duodenal obstruction comprise a variety of lesions, many of them complicated in type. The three cases described herein, on the other hand, presented simple and similar clinical manifestations and anatomic findings and responded to relatively simple operative procedures. Because of this simplicity, the details of the experiences of these three patients are presented.

In 1932, Ladd¹ described 11 cases of congenital duodenal obstruction over half of which were identical with the three cases herein described. Ladd was able to find in the literature, only ten cases successfully treated. The obstruction was located in the terminal duodenum and upper end of the jejunum and was "extrinsic," being caused by congenital bands plus a twisting of the entire small intestine just below the ligament of Treitz. Inasmuch as the cecum lay in the upper left quadrant these cases represented incomplete rotation of the intestines as mentioned in greater detail below. In regard to the operative procedure he stated "Though shocking, we feel that the only way to reduce the volvulus is by delivering the whole small bowel and untwisting it." Of the cases of malrotation which were operated upon, untwisting of the volvulus and cutting of bands was followed by cure in all, in one baby a gastro-enterostomy was performed with a fatal outcome. In a more recent report, Ladd² increased his series by 23, with 19 recoveries, and describes in more detail his operation for this (extrinsic) type of duodenal obstruction as a "transposing operation," emphasizing that reduction of the volvulus alone is not sufficient to permanently relieve the obstruction. The bands which impinge on the duodenum must be cut, thus allowing the cecum and ileum to be transposed toward their normal position in the right lower quadrant. Still more recently, Miller³ cited a number of congenital obstructions but only a few were of the type herein described. McIntosh

* Read before the St Louis Surgical Society, April 19, 1939, at St Louis, Mo
Submitted for publication November 6, 1939

and Donovan⁴ described a number of cases of disturbances of rotation, many quite similar to those of the extrinsic type described by Ladd and to those described herein

Inasmuch as the important feature in these cases seems to be a disturbance in rotation, it appears important to refer to Dott⁵ who, in 1923, presented a detailed discussion of malrotation with excellent charts illustrating three types of derangements corresponding to defects in the three stages of rotation. According to this description the present cases fell into the third group. Dott describes three of his own cases all of which died following operation, they presented much more complicated lesions than the ones herein described. Based upon the three stages of rotation the present cases would seem to be due to a failure of rotation only in the third stage, wherein,

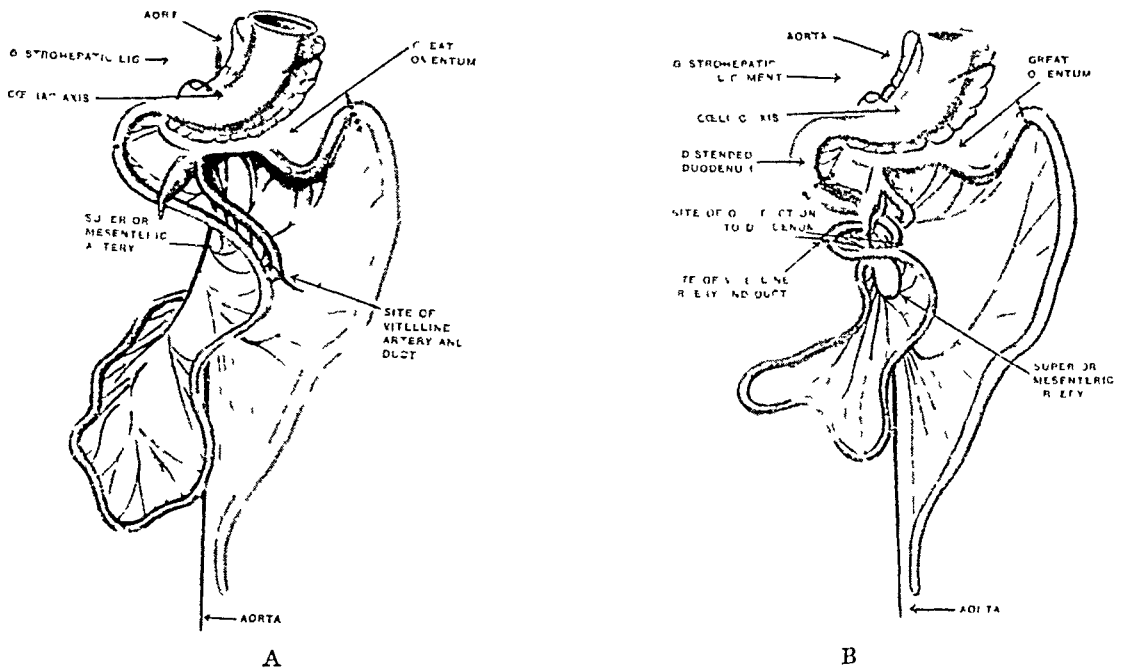


FIG 1—(A) represents arrested rotation of the third stage, and shows the close approximation of the ileum and upper jejunum with a slight twist of the prearterial segment through 90° (B) represents a further step in the twist producing a volvulus of the entire small intestine (Reproduced from Dott⁵)

normally, the cecum and ileum leave their position in the upper left quadrant and continue in their rotation toward the right lower quadrant. When this stage is arrested the ileum (and cecum) remain attached to the jejunum and from this single point the entire small intestine hangs—thus enabling it to become twisted (Fig 1). The twist or volvulus of itself is undoubtedly able to produce the duodenal obstruction although it is probable that the bands add to the completeness of the occlusion. The bands are also important in the pathogenesis in so far as they are attached to and fix the terminal ileum thus preventing the cecum and ileum from occupying their normal position in the right lower quadrant (Fig 2).

CASE REPORTS

Case 1—Hosp No N1972 Male, age 16 days. Since birth, there had been persistent bile stained vomiting, the weight dropped from seven pounds six ounces (3.3 Kg)

to six pounds four ounces (2.8 Kg) On admission, the general condition was good but the next day he suddenly became listless, the skin dry and inelastic. A diagnosis was made of duodenal obstruction and an operation performed. Through a right rectus incision, a tremendously dilated duodenum was found. The entire small intestine was collapsed and the cecum and appendix were found in the left upper quadrant. A twist, just distal to the ligament of Treitz, was found involving all of the small intestine, this was corrected by rotating the entire small intestine in a counter-clockwise direction. The ligament of Treitz could not be explored sufficiently because of the patient's poor general condition, which necessitated an immediate termination of the operation. On return to the ward the patient was in shock but recovered completely with the administration of fluids and a transfusion. On discharge, the patient was taking feedings well, and gaining in weight.

At five months of age the patient was admitted a second time because of recurrence of vomiting which ceased on thickened feedings. Roentgenologic examination showed no obstruction and a barium enema canalized to the hepatic flexure.

Two weeks later patient was admitted for a third time, with a history of persistent vomiting of several days' duration. A roentgenogram showed a complete obstruction at the terminal duodenum. A second operation was carried out, this time an upper left rectus incision was employed. The small intestine was eviscerated and found to be twisted as at the previous operation. The volvulus was reduced by untwisting the intestines in a counter-clockwise direction. The mesentery was the site of a tremendous edema. At the hepatic flexure the transverse colon turned sharply on itself so that the cecum lay in the upper left quadrant. The ileum was then found lying along the beginning jejunum and attached to it by well developed fibrous bands. These were severed, whereupon it became possible to return the cecum and terminal ileum toward the right lower quadrant. After division of the band, a definite groove could be seen at the beginning jejunum above which the duodenum was tremendously dilated. Recovery was entirely uneventful, and the patient remained well up to the present time (two years).

Case 2—Hosp No 02129 Female, age 1 month. There was a history of bile stained vomiting during the first 12 days of life, no vomiting for the next week, but persistent vomiting since. On admission, the baby was prostrated, dehydrated and exhibited convulsive movements during which she became quite cyanotic. Rectal bleeding was also observed. A roentgenogram following the ingestion of a barium meal showed a characteristic picture of obstruction at the terminal duodenum. The general condition of the patient was only slightly improved by conservative measures, and two days after admission operation was performed, employing local followed by general anesthesia. An upper left rectus incision was made, the cecum was found in the upper left quadrant with the appendix curled around the beginning jejunum. The entire small intestine was collapsed, it was eviscerated and a twist found and corrected by rotation in a counter-clockwise direction. No cause was found for the rectal bleeding except the volvulus. The general condition of the patient did not permit an adequate dissection of the ligament of Treitz, and the abdomen was closed. The change following the operation was spectacular, the color improved, breathing became more regular, the cry vociferous. The patient was discharged 12 days later, having gained one pound nine ounces (700 Gm).

At six weeks of age, the patient was admitted a second time and the feeding formula was adjusted. The baby remained well for one month, when she was readmitted for a third time, with a history of an occasional vomiting until two days before admission when she vomited everything. She was treated conservatively for one week, when it became obvious that the obstruction had recurred. A second operation was undertaken through the same upper rectus incision. A large postoperative band was found occluding the jejunum. There was also a recurrence of the twist. Exploration at the ligament of Treitz did not seem to reveal any obstructing band, and the abdomen was closed without doing anything further. The patient was discharged entirely well, with no further

vomiting, and remained well for another month, during which time she gained two pounds (1 Kg) in weight

The patient was admitted a fourth time because of multiple furuncles about the head, which were treated and healed in about three weeks. Just before she was about to be discharged she suddenly developed persistent vomiting, and roentgenologic examination showed a recurrence of the obstruction at the terminal duodenum. The general condition of the patient was excellent at this time. A third operation was carried out through the old upper rectus incision, the small intestine was eviscerated and found to be slightly distended, unlike its previous appearance. The mesentery was edematous and lymph nodes tremendously engorged. Visible lymph had accumulated beneath the peritoneum and had extended up the ligament of Treitz. Several bands were producing partial obstruction but upon careful exploration of the beginning of the jejunum it was apparent that an intermittent volvulus had been responsible for most of the changes noted. Further dissection revealed definite congenital bands between the beginning of the jejunum with the terminal ileum which had not been severed at the previous operations.

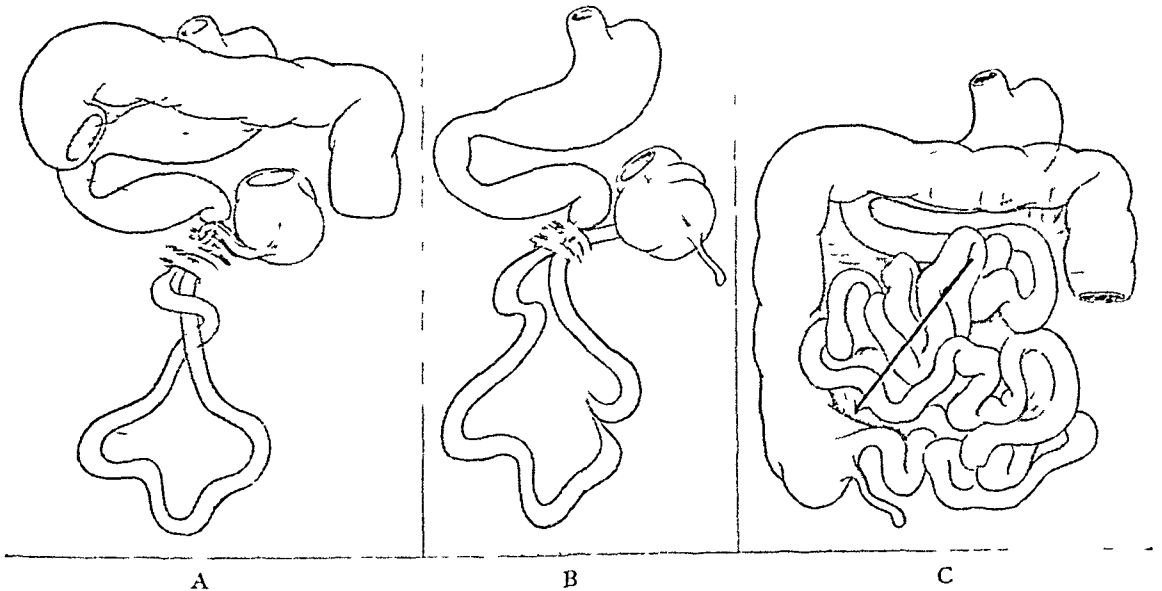


FIG 2—Diagrammatic sketches from the findings in Case 3.
(A) Note the dilatation of the duodenum above the bands and the volvulus which has been partly untwisted.
(B) The volvulus has been entirely reduced and the bands are ready to be cut.
(C) The bands have been cut and the cecum replaced toward the right lower quadrant in the direction indicated by the arrow.

These bands were cut extensively up to the point where the dilated duodenum became suddenly constricted. This resection permitted replacement of the cecum toward the right lower quadrant aided by the rotation of the entire small intestine in a counter-clockwise direction. Recovery from this operation was uneventful and patient has remained entirely well (one year).

Case 3—Hosp No 0859 Male, age 5 days. There was a history of persistent bile stained vomiting since birth. A roentgenogram, following the ingestion of a barium meal, revealed a characteristic obstruction at the terminal duodenum. The patient was treated conservatively for seven days and then operated upon, under general anesthesia, through an upper left rectus incision. The entire small intestine was collapsed but twisted, it was eviscerated and rotated in a counter-clockwise direction. The upper left quadrant was then carefully explored. The cecum lay in close relationship to the ligament of Treitz, the appendix being curled around the beginning of the jejunum. A band was found binding the jejunum to the ileum. This was cut extensively, until the dilated duodenum was reached. After this it was possible to mobilize the cecum and partially

replace it in the right lower quadrant (Fig 2) The abdomen was closed and recovery was uneventful There has been no further vomiting since operation (one year)

Discussion—Very little can be added to the clinical description and operative treatment recorded by Ladd^{1, 2} From the cases herein reported, as well as from those described by Ladd, one may say that incomplete rotation with volvulus produces manifestations which can be readily recognized and readily corrected

The most important symptom produced by such a lesion is persistent bile stained vomiting, beginning shortly after birth but in some cases interrupted by periods during which all food is normally retained Undoubtedly, this is possible because the twist in the intestines may become spontaneously, though only temporarily relieved During periods of obstruction visible gastric peristalsis may be seen passing from left to right, just as is true in pyloric stenosis If the baby is examined roentgenologically, no dilated loops of intestine are to be seen but a dilated stomach and duodenum can often be identified, if barium is given by mouth the shadows cast by the stomach and duodenum are clear and characteristic Significant, too, is the absence of general abdominal distention, the fulness in the upper abdomen can be made to disappear on aspiration by lavage of the gastric and duodenal contents

The general manifestations of dehydration are produced if vomiting is sufficient to result in anhydremia In addition to this, attacks of prostration and listlessness may occur similar to those seen in intussusception This is doubtless due to circulatory changes produced by an especially severe twisting of volvulus In one of the present cases passage of blood per rectum occurred, suggesting, too, circulatory obstruction produced by the volvulus

Once the diagnosis is made, unless signs promptly disappear, celiotomy is indicated General anesthesia and an adequate incision are necessary An upper left rectus approach leads most readily to the ligament of Treitz which is the seat of the lesion Much time is saved and unnecessary intraperitoneal trauma avoided by prompt evisceration of the entire small intestine Though, at first consideration, this procedure seems to be too radical, the advantages gained far outweigh the moderate shock it undoubtedly produces In the first place, evisceration is really essential in order to untwist the volvulus by rotation in a counter-clockwise direction In the second place, evisceration permits adequate exposure of the ligament of Treitz, which is necessary in order to sever the bands obstructing the terminal duodenum and the upper jejunum Moreover, since these bands are also attached to the terminal ileum, by dividing them it becomes possible to mobilize the cecum and ileum, releasing their fixation to the upper left quadrant and allowing them to be placed toward their more normal position in the right lower quadrant On the basis of the present observations (Case 2) this is essential in order to prevent recurrence of the volvulus Gastro-enterostomy is unnecessary in this type of obstruction and if carried out adds to the risk of the operation

SUMMARY—Three cases are described of duodenal obstruction in infancy, due to volvulus of the entire small intestine, plus congenital (extrinsic)

bands occluding the terminal duodenum and upper jejunum. The defect seems to be a failure in the third stage of intestinal rotation associated with an attachment of the terminal ileum to the upper jejunum in the upper left quadrant. Recovery followed in all three cases after carrying out Ladd's operation, *i e*, untwisting the volvulus plus cutting the extrinsic bands attached to the upper jejunum and terminal ileum.

REFERENCES

- ¹ Ladd, W. E. Congenital Obstruction of the Duodenum in Children. *New Eng Jour Med*, 206, 277, 1932.
- ² Ladd, W. E. Congenital Duodenal Obstruction. *Surgery*, 1, 878, 1937.
- ³ Miller, E. M. Bowel Obstruction in the New Born. *ANNALS OF SURGERY*, 110, 587, 1939.
- ⁴ McIntosh, R., and Donovan, E. J. Disturbances of Rotation of Intestinal Tract. *Am Jour Dis Child*, 57, 116, 1939.
- ⁵ Dott, N. M. Anomalies of Intestinal Rotation. Their Embryologic and Surgical Aspects. Report of Five Cases. *Brit Jour Surg*, 11, 251, 1923.

PLASMA TRANSFUSION IN EXPERIMENTAL INTESTINAL OBSTRUCTION

JACOB FINE, M D

BOSTON, MASS

AND

SAMUEL GENDEL, M D

LOS ANGELES, CALIF

FROM THE SURGICAL RESEARCH LABORATORY, BELT ISRAEL HOSPITAL AND THE DEPARTMENT OF SURGERY,
HARVARD MEDICAL SCHOOL, BOSTON, MASS

WE have recently published¹ evidence that in experimental intestinal obstruction plasma is lost to an extent sufficient in itself to cause death. Most of this plasma loss is attributable to the factor of distention alone. Some loss of plasma due to dehydration occurs during the course of the experimental period but it is not of sufficient magnitude to be significant in the death of the distended animal. Previous studies^{2, 3} showed that loss of blood, fluid and electrolytes into the intestinal lumen, bowel wall, and peritoneal cavity was not responsible for the plasma loss or for the rapid death from obstruction with distention. The possible deleterious influence of noxious nerve stimuli originating in the distended bowel was also excluded from responsibility. Furthermore, it was found that animals whose empty small intestines were obstructed and distended did not survive as long as others which were obstructed but not distended, and that the survival time was shortened in proportion to the height of the intra-intestinal pressure. The one uniform finding which constituted an adequate explanation for the quicker death of the distended animals was a progressive and extensive loss of blood plasma.

We have, to date, no conclusive answer as to the mechanism by which distention produces plasma loss, although our studies suggest that part of the plasma is forced into the interstitial spaces of the pelvis and lower limbs because of impeded venous return from these areas. In any case the obvious inference from these observations, if they are correct, is that transfusions of plasma, in sufficient volume to replace the plasma which is lost, should have a favorable influence upon the course of the process. In this communication are described the results of experiments designed to elucidate this question.

Method—Dogs were used exclusively. Their normal plasma and whole blood volumes were determined under intraperitoneal nembutal anesthesia immediately preceding or several days in advance of the experiment by a technic already described¹. After 24 hours of starvation, but with water allowed, the dogs were anesthetized by intraperitoneal nembutal. The pylorus was ligated and the ileocecal valve was divided, its distal end inverted

and a glass cannula tied into its proximal end. The cannula was brought out through a stab wound after closing the abdominal incision and connected to a Perusse pressure bottle. The entire small intestine was kept continuously inflated with air at a pressure of 20 cm. of water (a level consistent with that observed in clinical and experimental obstruction) until death occurred.

Plasma for transfusion was obtained from large, normal, healthy dogs by exsanguination under sterile precautions. Fifty cubic centimeters of a sterile 25 per cent sodium citrate solution in physiologic saline was added to each 450 cc. of blood and stored for from one to three days at a temperature varying from 0 to 4° C. Before use the supernatant plasma was siphoned off and diluted to two or three times its volume with physiologic saline to reduce its viscosity so that it would run without clotting. Some of the specimens used showed a slight hemolysis.

Immediately after obstructing and distending the intestine, plasma (plus two to three times its volume of physiologic saline) was run into the femoral vein at a rate of five to eight drops per minute until its administration was purposefully interrupted or until the supply was exhausted or until the animal died. The volume transfused in a given time differed from one animal to another in accordance with the calculated loss in plasma volume to be anticipated.

Determinations of plasma and whole blood volumes were made at intervals as convenience and the circumstances of the experiment allowed.

In order to determine the specific value of plasma as against other fluids which are considered useful for restoration of lost fluid, intravenous physiologic saline (in one experiment 6 per cent acacia [Lilly] was added) was given to different dogs and its effect on plasma volume and survival time noted.

The details of each experiment are listed in Table I. The significance of the results can best be appreciated by discussing each experiment individually.

DOGS RECEIVING PLASMA TRANSFUSIONS

Experiment I—This dog received plasma continuously from the beginning of the experiment until the thirty-ninth hour of distention. Death occurred five hours after the plasma was discontinued. The total survival time of 43 hours is in contrast to an average survival time of 20.8 hours for distended dogs not receiving plasma.¹ Two hundred cubic centimeters of plasma was given during the first five hours, with a resultant increase of 7 per cent in plasma volume instead of an expected average fall of 35 per cent after a similar interval of distention in dogs not receiving plasma. There was a simultaneous decline in total blood volume of 6 per cent because of a 15 per cent loss in red cell volume, which is presumably, at least in part, a relative rather than an absolute loss. Distended dogs not receiving plasma uniformly show a rise in hematocrit averaging 37.8 per cent after four to six hours, but this dog showed a fall, also relative, of 12 per cent. An additional 250 cc. of plasma was administered by the end of the twenty-third hour of distention. The fall in plasma volume at this time was 3 per cent in contrast to an average fall, after approximately the same interval, of 55 per cent in distended dogs not receiving plasma. After the thirty-eighth hour, by which time the dog had received a total of 650 cc. of plasma (plus the diluent of 1,300 cc. of physiologic saline), the plasma transfusion was stopped. Death occurred five hours later.

COMMENT—In a previous series of 11 dogs with obstruction and distention but no plasma transfusion, seven died in 20 hours or less. The longest survival time was 30 hours. The fall in plasma volume in those dogs surviving as long as 23 hours was never less than 45 per cent, an amount sufficient to cause death. Since the fall in Dog I of the present series after this interval was only 3 per cent, we conclude that plasma transfusion was responsible for prolonging the survival time to approximately twice the average in those dogs which did not receive plasma.

Experiment II—After 20 hours of obstruction and distention during which 350 cc of plasma was infused, the plasma volume increased 32 per cent and the hematocrit fell 16 per cent, results which are substantially the same as in Experiment I. An additional 150 cc of plasma was administered during the next 16 hours, but, unfortunately, a plasma volume measurement was not obtained until six hours after the plasma was discontinued (because of exhaustion of supply). During this interval of distention without plasma replacement a 39 per cent fall in plasma occurred and the dog died 14 hours later, with a total survival time of 56 hours, which is not far removed from the expected survival time of an intact dog under continuous intraperitoneal nembutal anesthesia.¹ Had the cannula in the ileum not perforated the wall of the intestine by mechanical friction, with resulting terminal, extreme pneumoperitoneum, the survival time might have been even more prolonged.

COMMENT—It will be noted that the total volume of the transfused plasma exceeded the dog's own plasma volume. In spite of this a 39 per cent loss of plasma occurred within six hours after the plasma transfusion was discontinued.

It is apparent from this experiment that the plasma loss caused by distention continues uninterruptedly so long as distention is maintained, and that the plasma infused serves only to replace what is lost. Evidence is available that slowing or reversal of the process by which plasma is lost can be achieved by decompressing the intestine.⁴ If, while distention persists, the plasma loss proceeds at a rate exceeding that of replacement, the fall in plasma will go on to cause a fatal issue. This is indicated in Experiment III.

Experiment III—The original plasma volume of this dog was 656 cc. According to our previous data the expected loss from distention in four to six hours would equal 229 cc. Only 75 cc was transfused during the first seven hours and a fall of 30 per cent in plasma volume was observed. At this rate of plasma loss the animal's survival time would hardly have reached its actual value of 46 hours. We attribute this survival period to the fact that an additional 225 cc of plasma was administered between the seventh and the thirtieth hours. Death occurred six hours after plasma administration was stopped.

The effect of supplying plasma in excess of the expected calculated plasma loss is illustrated in the next experiment.

Experiment IV—In this dog, with an initial plasma volume of 517 cc, the expected loss after four hours without plasma transfusion would be 181 cc. Two hundred cubic centimeters of plasma was administered with a resulting gain in plasma volume of 10 per cent. The hematocrit fell 20 per cent. Without plasma transfusion an increase in the hematocrit of some 45 per cent would be anticipated. Similarly, after 23 hours, when a total of 500 cc of plasma had been given (216 cc more than the average expected loss when plasma is not transfused), a 19 per cent increase in plasma volume and a 31

per cent decrease in hematocrit were observed (In this, as in one other distended animal receiving plasma, urine was excreted during the experiment and the tissues were slightly edematous at autopsy) Although an additional 100 cc of plasma was administered during the next ten hours, the dog died after 43 hours, surviving only nine hours after the plasma transfusion was interrupted

COMMENT—It is apparent, therefore, that when plasma is administered in adequate quantity it serves to sustain the distended dog while it is being administered and for a variable, but only short interval afterward It should not be surprising that the survival time is not longer, if one bears in mind that in addition to the deteriorating effect of the continuing loss of plasma, the limit of survival of an intact dog under continuous intraperitoneal nembutal anesthesia is being approached¹

Further evidence that plasma continues to be lost so long as distention is maintained may be observed in Experiment V

Experiment V—One hundred cubic centimeters of plasma was transfused during the first five hours of distention This quantity is insufficient to balance the expected calculated loss of about 297 cc (35 per cent of 894 cc) Consequently a drop in plasma volume of 16.4 per cent was observed after the fifth hour During the next nine hours 300 cc more of plasma was administered in order to approximate the expected total calculated loss (400 cc) after 14 hours of distention The plasma infusion was then stopped and seven hours later, or 21 hours after the onset of the distention, the plasma volume had fallen only 6.4 per cent below its value after the fifth hour, which clearly demonstrates the sustaining function of the infused plasma But in a further six hours the plasma loss had reached 47.9 per cent, with death following nine hours later, a total survival time of 36 hours

COMMENT—We consider that this death occurred six hours earlier than the next earliest death in this group of five animals because the plasma transfusion was given for only 14 hours instead of for 33 or more hours as in the other four dogs

The data in the next two experiments are incomplete, but are of value in connection with the general thesis of this paper

Experiment VI—The changes in plasma volume in this dog could not be measured because the donor's plasma had been partly diluted with distilled water which caused marked hemolysis This prevented photo-electric colorimetric determinations of plasma volume In spite of the hemolysis, the presence of severe strangulation of the bowel and a terminal pneumoperitoneum due to rupture of the bowel by the glass cannula,* the dog survived 38 hours, having received 400 cc of plasma during the first 19 hours

COMMENT—This is in marked contrast to the survival time of ten, 12 and 18 hours, respectively, of a previously reported group of three dogs with venous strangulation and distention, but no transfusion of plasma¹

Experiment VII—A week before the experiment this dog's control plasma volume was 994 cc, but when the experiment was started the dog was very sick Upon opening the abdomen, generalized peritonitis was found He was, nevertheless, distended for four and one-half hours, during which time he did not receive plasma At the end

* We subsequently learned to prevent this by using, instead of an ordinary glass tube with an open end, a cannula with a balloon tip containing numerous perforations

TABLE I

THE EFFECT OF CONTINUOUS INTRAVENOUS INFUSION OF PLASMA UPON THE SURVIVAL TIME, THE PLASMA AND WHOLE BLOOD VOLUME, AND THE HEMATOCRIT IN DOGS WITH CONTINUOUS DISTENSION OF THE ENTIRE SMALL INTESTINE AT A PRESSURE OF 20 CM OF WATER

Dog No	Weight (in Kilos)	Survival Time (in Hours)	Hours After Beginning Distention	Total Cumulative Volume of Infusate (in Cc)	Plasma Volume (in Cc)	Change in Plasma Volume (in Per Cent)	Total Blood Volume	Change in Total Blood Volume (in Per Cent)	Red Cell Volume (in Cc)	Change in Red Cell Volume (in Per Cent)	Hematocrit (in Per Cent)	Change in Hematocrit (in Per Cent)	Plasma Total Red Blood Cell Volume (in Per Cent of Body Weight)	Remarks
1	16.8	43	0 5 23 38	705 755 430 650	705 755 680	+7.0 -3.0	1,639 1,540 1,402	-6.0 -14.0	934 785 722	-15.0 -22.0	57.0 50.0 51.5	-12.0 -11.0	4.2 4.5 4.0 9.7 9.1 8.4 5.5 4.6 4.4	
2	9.5	56	0 20 36 42	451 350 300	451 466 276	+3.2 -39.0	902 804 613	-10.0 -32.0	451 338 371	-25.0 -18.0	50.0 42.0 55.0	-16.0 +10.0	4.7 4.9 2.9 9.4 8.4 6.5 4.7 3.5 3.6	Severe pneumoperitoneum at autopsy
3	14.4	46	0 7 38	75 300	656 458	-30.0	1,339 904	-32.0	683 446	-34.0	51.0 51.5	0.0	4.6 3.2 9.3 6.3 3.1 4.7 3.1	Distention started 12 hours after obstruction, without distention
4	16.1	42	0 4 23 33	200 500 600	517 575 718	+10.0 +19.0	1,229 1,064 1,197	-11.0 -1.0	712 489 479	-31.0 -34.0	58.0 46.0 40.0	-20.0 -31.0	3.2 3.5 4.3 7.6 6.6 7.3 4.3 3.0	
5	17.5	36	0 5 14 21 27	100 400	849 709	-16.4	1,439 1,266	-12.0	500 557	-5.5	41.0 44.0	+6.4	4.8 4.0 8.2 7.2 3.4 3.2	
6	11.8	38	0 19	400	654 442	-22.9 -47.9	1,257 945	-12.6 -34.5	603 503	+2.1 -14.0	48.0 53.0	+11.5 +22.6	3.7 2.5 7.1 5.7 3.4 3.2	Venous strangulation of intestine, pneumoperitoneum, hemolyzed blood
7	18.1	23 3/4	0 4 1/2 23	250	904? 620 718	-37.0? -27.5?	1,713? 1,140 1,408	-33.0? -22.0?	710? 520 790	-26.0? +9.0?	58.0? 46.0 49.0	-20.0? -15.0?	5.4? 3.4? 3.9? 9.4? 6.3? 7.7? 4.0? 2.0? 3.8?	Pertontitis at beginning of experiment. In extremities at the end of five hours of distention. Plasma infusion started at that time.

of this interval he appeared moribund. Although the resulting drop in plasma volume of 37 per cent is about what may be expected in an animal without peritonitis, it is an unreliable determination because the initial control volume was probably quite different from the value obtained a week previously. But it was used as a base line for the determination of subsequent changes.

The animal then had 100 cc of plasma in physiologic saline administered rapidly, with immediate and marked improvement in his general condition. Plasma was continued intravenously for the next 18½ hours, when he died, having received a total of 250 cc of plasma. The plasma volume shortly before death had been increased some 16 per cent above the level prevailing after four and one-half hours of distention.

COMMENT—The rapid deterioration caused by the first four and one-half hours of distention is suggestive of the clinical experience that distention seriously increases the burden of peritonitis. The prolongation of life for 18 hours after what were, apparently, terminal respiratory efforts demonstrated the protective effect of plasma transfusion.

DOGS RECEIVING INTRAVENOUS SALINE

It will be recalled that in all of the experiments described the plasma was transfused after having been diluted with two or three volumes of physiologic saline in order to permit the plasma to run smoothly and uniformly without clotting. From earlier data, previously reported, we were convinced that dehydration and dechlorination were not substantial factors in the early death of dogs obstructed and distended in accordance with our technic. To further substantiate this belief, and to show whether or not there was any protective virtue in the physiologic saline administered with the plasma in the experiments with which we have been here concerned, five dogs were treated with physiologic saline alone. In Experiments VIII, IX and X (Table II) physiologic saline injections were administered in amounts and at rates equivalent to those given with plasma in Experiments I to VII (Table I). In Experiments XI and XII, 500 cc was injected rapidly at the end of the fourth and thirteenth hours of distention, respectively. The average survival time in these five dogs was 15.8 hours, which is in contrast to 43.5 hours for the first six dogs of this series receiving plasma and saline, but quite comparable to the average survival time (20.8 hours) of dogs receiving no plasma or saline.

This amply confirms our previous conclusion that dehydration and dechlorination were not significant factors in the death of our distended animals, and shows that physiologic saline exerts little or no protective effect. We are in agreement with others (Taylor, Weld and Harrison⁵) who believe that when and if dechlorination occurs in the course of intestinal obstruction, it is an incidental factor which deserves correction, but is by no means a crucial factor in the lethal effects of obstruction.

In one experiment with 6 per cent acacia added, no protection was afforded the animal, as judged by the survival time (Table II).

Discussion—The fact that distention is the central disturbing feature of uncomplicated intestinal obstruction is universally accepted. It is also gener-

TABLE II
THE EFFECT OF CONTINUOUS INTRAVENOUS INFUSION OF PHYSIOLOGIC SALINE UPON THE PLASMA AND BLOOD VOLUME,
HEMATOCRIT AND SURVIVAL TIME OF DOGS WITH INTESTINAL OBSTRUCTION AND CONTINUOUS
DISTENTION OF THE ENTIRE SMALL INTESTINE AT A PRESSURE OF 20 CM OF WATER

Dog No	Weight (in Kilos)	Hour After Beginning Distention	Type and Amount of Solution Given (in Cc)	Survival Time (in Hours)	Plasma Volume (in Cc)	Reduction in Plasma Volume (in Per Cent)	Total Blood Volume (in Cc)	Reduction in Total Blood Volume (in Per Cent)	Red Blood Cell Volume (in Cc)	Change in Red Blood Cell Volume (in Per Cent)	Hematocrit (in Per Cent)	Remarks
8	18 2	12	Saline 750	12								
9	14 1	14	Saline 550	14								
10	18 0	0			665		1 279		614		48	Venous strangulation of entire small bowel
	12		Saline 800	15	382	43 0	1 009	21 0	627	+ 2 0	62	
	15		Saline 1 100									
11	23 6	0	Saline 500	18	1,090		2 180		1 090		50	Saline given in single dose instead of continuously after fourth hour of distention
	4				724	33 5	1 810	16 9	1,086	0 0	60	
12	11 0	0	Saline 500	20	655		1 101		446		41	Saline given in single dose instead of continuously after the thirteenth hour of distention
	13				358	45 3	745	32 3	387	- 13 2	52	
13	14 5	0	6% acacia in saline 300	11½								
	11½											

ally agreed that the correction of dehydration and electrolytic imbalance do not prevent death, and that death may occur before starvation becomes a significant factor, and before strangulation or peritonitis supervenes

We¹ have recently provided data to show that a fatal loss of plasma occurs as a direct consequence of increased intra-intestinal pressure, and that this plasma loss is independent of the loss of fluid or electrolytes into the intestinal lumen or wall or into the peritoneal cavity. Evidence was already at hand to show that the survival time of distended animals is inversely proportional to the height of the intra-intestinal pressure. We believe that this is due to a more rapid loss of plasma in animals with higher intra-intestinal pressures.

We do not insist that the loss of plasma is the only significant phenomenon in the lethal process. But it is the only one brought forward, thus far, which may be regarded as of basic importance. For, obviously, even if other primary mechanisms should in time come to be shown as operative in the death from intestinal obstruction, their circumvention will not substantially alter the course of the process so long as the plasma loss remains uncompensated.

The validity of the foregoing experimental observations on the therapeutic effect of plasma transfusions in intestinal obstruction and distention rests on the significance of the prolongation of the survival time from an average of some 20 hours to one of 40 or more. If plasma loss is the crucial factor, why should its replacement postpone death for only 40 or 50 hours, why not indefinitely? The answer is twofold. (1) The plasma transfusion was not continued until death occurred, it was interrupted six or more hours before death, and during this interval a sharp drop in plasma volume occurred. Had plasma replacement been carried on there is reason to believe that the survival time would have been even longer. (2) There are limitations on the survival time of an animal which must, in the nature of the experiment, be kept lying on its back continuously under the constant influence of an anesthetic. The survival time of an intact dog under these circumstances is a matter of some two to three days. Such a dog dies without a serious loss in plasma volume so that, presumably, transfusion of plasma would not prolong life significantly. It would be illogical to expect that the infliction of a still greater burden, even though to a large extent nullified, should permit survival for as long a period of time. Hence, we believe that the considerably longer period of survival achieved by plasma replacement is of primary significance and confirms our contention that the loss of plasma is a vital characteristic of the process of decline in intestinal obstruction.

SUMMARY—Five dogs subjected to intestinal distention at a pressure of 20 cm of water had plasma administered continuously, intravenously, to replace part or all of the anticipated loss of plasma as determined from previous data already published. Effective maintenance of the control plasma volume occurred when the supply of intravenous plasma was adequate. Interruption of the administration of plasma was followed by a drop in plasma volume sufficient to cause death. The survival time of these dogs was prolonged from

an expected average of 208 hours for distended dogs not receiving plasma, to 40 or more hours

The duration of life of similarly distended dogs which received intravenous physiologic saline but no plasma was not prolonged beyond the survival time of dogs receiving nothing parenterally. The survival time of one dog, which received acacia solution in saline, was about the same as that of dogs receiving saline alone.

CONCLUSIONS

(1) The intravenous injection of plasma, in amount adequate to replace that lost as a result of obstruction and distention of the empty small intestine, confers a protective influence sufficient to markedly prolong the life of the animal.

(2) The intravenous injection of physiologic saline, in amount sufficient, or more than sufficient to replace fluid lost under the conditions of our experimental technique, confers no noticeable benefit.

(3) Loss of plasma continues so long as distention continues in the obstructed small intestine of the dog. The extent of this loss, if uncompensated, is sufficient in itself to cause death, and is of primary importance in the pathologic physiology of intestinal obstruction.

REFERENCES

- ¹ Gendel, S, and Fine, J. The Effect of Acute Intestinal Obstruction on the Blood and Plasma Volumes. *ANNALS OF SURGERY*, 110, 25, July, 1939.
- ² Rosenfeld, L, and Fine, J. The Effect of Breathing 95 Per Cent Oxygen Upon the Intraluminal Pressure Occasioned by Gaseous Distention of the Obstructed Small Intestine. *ANNALS OF SURGERY*, 108, 1012, December, 1938.
- ³ Fine, J, Rosenfeld, L, and Gendel, S. On the Rôle of the Nervous System in Acute Intestinal Obstruction. *ANNALS OF SURGERY*, 110, 411, September, 1939.
- ⁴ Fine, J, Fuchs, F, and Gendel, S. The Effect of Decompression on the Plasma Volume Changes Induced by Distention of the Obstructed Intestine. *Arch Surg*. In Press.
- ⁵ Taylor, N B, Weld, C B, and Harrison, G K. Experimental Intestinal Obstruction. *Canad Med Assoc Jour*, 29, 227, 1933.

METASTATIC PULSATING TUMOR OF BONE SECONDARY TO
RENAL CARCINOMA

CASE REPORT

H E SHIH, M D ,

AND

SHAO-HSUN WANG, M D

PEIPING, CHINA

FROM THE DIVISION OF UROLOGY, DEPARTMENT OF SURGERY AND THE DEPARTMENT OF RADIOLOGY,
PEIPING UNION MEDICAL COLLEGE, PEIPING, CHINA

ADENOCARCINOMA, popularly known as "hypernephroma" or "Grawitz tumor," is the most common form of renal carcinoma. It is generally conceded that such tumors tend to metastasize to the osseous system. In a series of 63 cases, Geschickter and Copeland¹ found 22 instances, or 35 per cent, of skeletal metastases. The bones most frequently involved in the order of frequency were the humerus, spine, femur, pelvis, ribs, bones of foot, skull and sternum. The incidence of skeletal metastases in renal carcinoma, as observed in different clinics, is listed in Table I. Certain interesting features of an instance of this condition, recently observed in the Urologic Service of the Peiping Union Medical College Hospital, warrant this report.

TABLE I
INCIDENCE OF SKELETAL METASTASES IN RENAL CARCINOMA AS OBSERVED IN
SEVERAL CLINICS

Author	Clinic	Hyper-	Skeletal Metastases	
		nephroma No of Cases	No of Cases	Per Cent
Geschickter and Copeland ¹	Johns Hopkins Hosp	63	22	35.0
Garceau ²	Mass Gen Hosp	176	35	20.0
Dresser ³	Mass Gen Hosp	46	6	13.0
Judd and Hand ⁴	Mayo Clinic	367	11	3.0
Diez and Michans ⁵				50.0
Shih and Wang	P U M C	14	3	21.4

Case Report—M C Y, a Chinese male, age 68, was admitted to the hospital, in May, 1938, complaining of a painful swelling of the right wrist. He had first noticed a small, firm and painless swelling over the ulnar side of the right wrist in January, 1938. Intense pain developed when he attempted to reduce this mass by massage. The pain was constant and throbbing in character, and was aggravated by motion of the wrist. The dorsum of the hand became swollen soon afterward and the motion of the wrist became limited on account of the pain and edema. The tumor gradually increased in size and was observed to be pulsating from the time of the onset of the pain. In April, a similar tumor appeared in the left occipital region. It was moderately painful, definitely pulsating and slowly increasing in size. The patient's appetite was impaired and there was much loss of weight.

Only by careful review of the past history was it possible to disclose the fact that, in September, 1937, the patient had been seized by severe throbbing pain in the right upper abdomen which lasted throughout one night and was relieved by gentle massage. At the

same time a small, firm mass was first noticed in the right hypochondrium, which has persisted. The patient had three subsequent attacks of milder pain. There were no urinary symptoms except "hematuria" which had been present for several months ten years previously, and had recurred in a milder form shortly before admission.

Physical Examination—The patient's general condition was fair. The abdomen was found to be bulging in both flanks and shifting dullness was easily demonstrated. Under the costal margin, a firm, tender mass, about 10x10 cm., could be palpated in the region of the right kidney (Fig 1). This mass was not fixed but moved with respiration. The right hand was warmer than the left and its superficial veins were dilated. The distal end of the forearm was definitely enlarged, especially on the ulnar side (Fig 2). The circumference of the wrist at the level of the styloid process of the radius was 20.5 cm. on the right and 17.0 cm. on the left side. The swelling measured 11x8 cm. and felt cystic in some areas. All over this mass, expansile pulsation, synchronous with the heart beat, could be felt and a loud systolic bruit was audible. Flexion of the wrist and interphalangeal joints, pronation and supination of the forearm were much limited. Another cystic

FIG 1

FIG 2

FIG 3



FIG 1—Photograph showing the outline of the right kidney extending below the level of the costal margin.

FIG 2—Photograph showing the swelling over the distal end of the right forearm.

FIG 3—Photograph showing the outline of the swelling over the left occipital region.

swelling, slightly tender and also pulsating, was present in the left occipital region (Fig 3). Here again, a systolic bruit could be heard. The overlying scalp was normal.

The external genitalia and the prostate gland were essentially normal. The urine was clear and contained no pus cells. The renal function, as estimated by phenolsulphonphthalein excretion, was 60 per cent in two hours. The blood picture showed slight secondary anemia. The figures for the chemical constituents in the blood were within normal limits. The Wassermann reaction of the blood was negative. *Clinical Diagnosis*—Carcinoma of the right kidney with metastases to the skull, the right ulna and the peritoneum.

Cystoscopy revealed the interior of the urinary bladder to be normal. Ureteral catheterization demonstrated obstruction in the right ureter from which urine was not obtained. Bilateral retrograde urograms (Fig 4) showed a large tumor in the region of the right kidney, the calices and pelvis of which were not filled by the contrast medium.

Excretory urograms (Fig 5) made following the intravenous injection of 20 cc. of hippuran (12 Gm.) confirmed the previous findings. The right kidney was enlarged, showed calcified shadows in the lower portion, and gave evidence of having lost practically all of its excretory function. The left renal pelvis and calices were fairly normal in appearance and the function of this kidney seemed unimpaired.



FIG 4—Retrograde pyelogram showing a large tumor in the region of the right kidney, the pelvis and calices of which have not been filled by the contrast medium. The arrow points to areas of calcification.

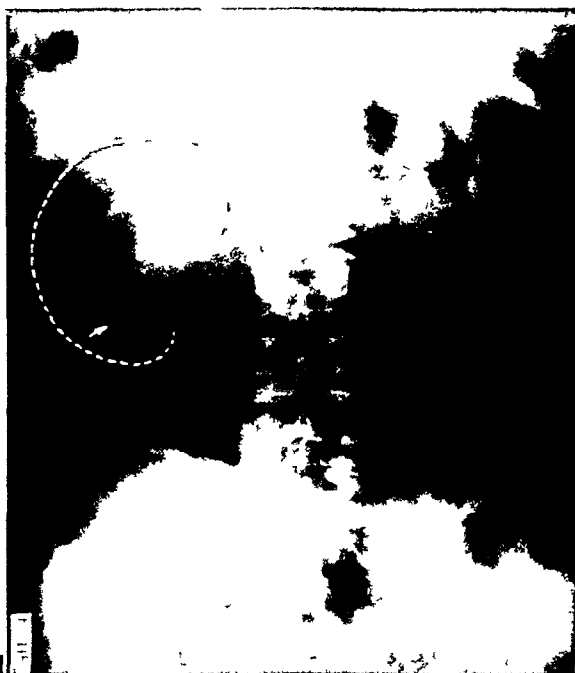


FIG 5—Excretory pyelogram which confirms the retrograde pyelographic findings. Note absence of excretion of the dye on the right side.



R

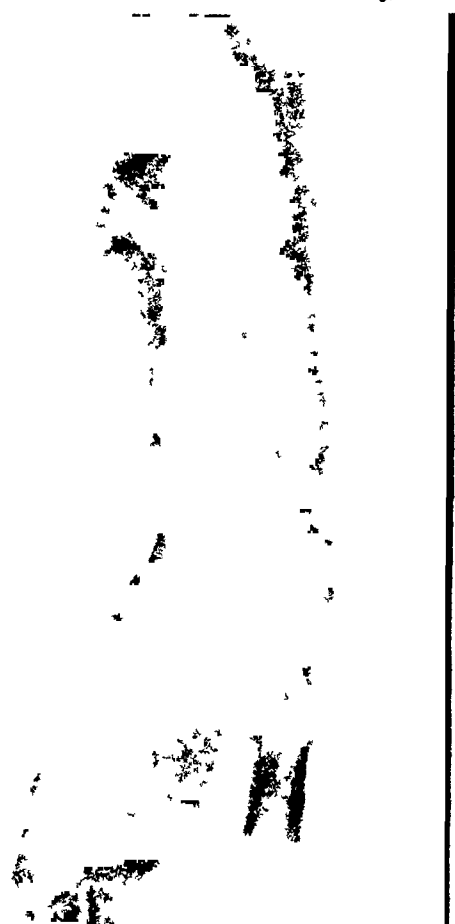


FIG 6—Roentgenograms of the right wrist showing destructive lesion of the lower end of the ulna.

Roentgenologic examination further revealed (1) An irregular erosion, 2.5 cm in diameter, in the right occipital region, involving both tables of the skull, and (2) destruction and absorption of the distal end of the right ulna (Fig 6). Careful roentgenologic examination of the chest and the spine revealed no evidence of metastasis to these structures.

A needle biopsy from the tumor of the right ulna was made. *Microscopic Examination* (Fig 7) revealed epithelial tumor cells which showed a great tendency to form irregular glandular structures separated by a scanty amount of stroma or by capillaries. The tumor cells were cuboidal or columnar with pale and granular cytoplasm which contained a number of small vacuoles. The nuclei were round or oval, generally situated toward the base and contained much chromatin material. Occasional mitotic figures were found. *Histologic Diagnosis* Adenocarcinoma, which, in view of the clinical and roentgenologic data, was believed to have arisen from the kidney.

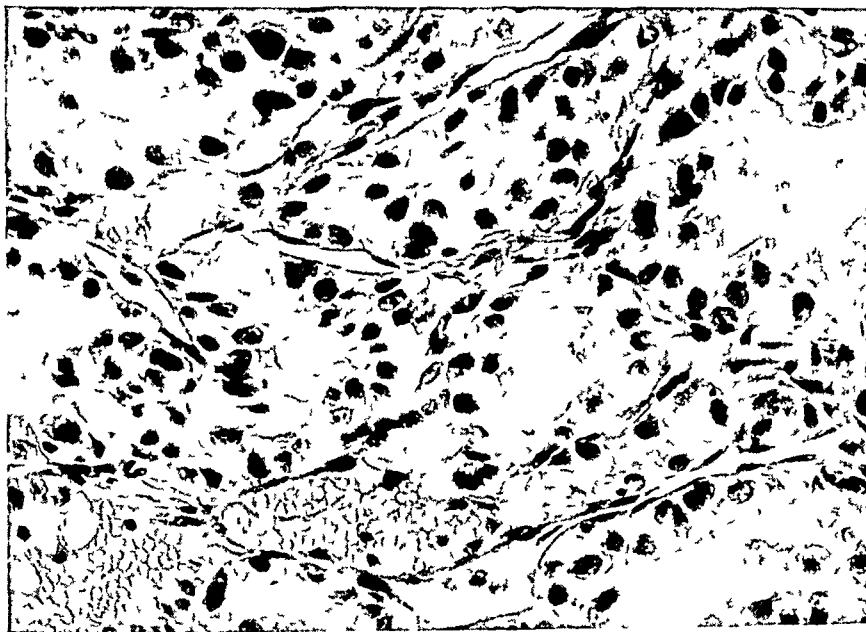


FIG 7—Photomicrograph of the metastatic tumor in the right ulna. Note the tendency to form glandular structures. (×295)

On account of his age and the extent of the lesions, the patient refused treatment and returned home where he died four months later.

Clinical Considerations—This case presents several striking and interesting features. In the first place, it illustrates very well the point that frequently it is the metastatic lesion in the bone which first prompts the patient to seek medical treatment. Diez and Michans⁵ state that in 50 per cent of their cases, skeletal metastasis was the first clinical manifestation of an otherwise symptomless hypernephroma. Occasionally the primary tumor may remain silent for a long period, even after a pathologic fracture, due to secondary tumor in bone, has occurred.

Second, the finding in the ulna of a metastatic lesion from any tumor is in itself exceedingly rare. It has been stated³ that "any bone in the body may be involved but metastases distal to the humerus and femur are infrequent." Risley⁶ states that bone metastasis occurs almost entirely proximal to the elbow and knee joints. In an attempt to explain this phenomenon, Piney⁷ showed

that metastatic deposits in bone are due to arterial or capillary embolism, that the location of metastases seems to conform to the anatomic distribution of the red marrow and that after puberty the red marrow extends only as far as the upper ends of the humerus and femur. The literature records only 13 instances in which the skeletal metastases from hypernephroma were located distal to the humerus and femur (Table II).

Third, the pulsating character of the metastatic tumor* is noteworthy. Lesions in the bone secondary to hypernephroma are often very vascular, giving a definitely expansile pulsation and audible bruit, so that they may be mistaken for aneurysms. Eschner,¹⁴ MacLeod and Jacobs,¹⁵ Dresser,³ Cabot,¹⁶ Crile, Jr.,¹⁷ and Roth and Davidson¹⁸ have reported six instances of pulsating tumors of the sternum secondary to a renal hypernephroma, and an aortic aneurysm was suspected in practically every instance. Storath,¹⁹ and Diez and Michans⁷ have reported instances of pulsating metastases from hypernephroma to bones of the nose and foot. The latter authors state that 35 per cent of skeletal metastases secondary to hypernephroma show pulsation and give an easily audible systolic bruit. It seems reasonable, therefore, to suggest that any pulsating tumor of the skeletal system should be thoroughly investigated with this possibility in mind, even in the absence of clinical manifestations of a primary renal tumor.

TABLE II

RECORDED INSTANCES IN WHICH SKELETAL METASTASES FROM HYPERNEPHROMA WERE LOCATED DISTAL TO THE HUMERUS AND FEMUR

Author	Location	No. of Cases
de Massary and Weill ⁸	Phalanges	1
Garceau ²	Metacarpals	1
Nitch ⁹	Ulna	1
Hand and Broders ¹⁰	Radius	1
Geschickter and Copeland ¹	Tibia	1
Garceau ²	Tibia	1
Dresser ³	Tibia	1
von Bergmann ¹¹	Tibia	1
Pool ¹²	Fibula and tibia	1
Geschickter and Copeland ¹	Bones of foot	2
Diez and Michans ⁵	Metatarsals	1
Sabolotnow ¹³	Tarsals and metatarsals	1
Total		13

Fourth, the roentgenologic interpretation of the lesion in the ulna was not easy in this instance. Baetjer and Waters²⁰ state that this type of tumor is of medullary origin and that it is impossible to differentiate it from other medullary nonbone producing growths. Gibson and Bloodgood²¹ remark that "As regards the roentgenologic findings, these may be summed up as resembling those of a central sarcoma of the bone. There is never any production of new bone, the cortex may be expanded, there is usually rarefaction of bone in the

* Similar pulsating skeletal metastases have also been recorded in cases of primary carcinoma of thyroid.

neighborhood, and the metastatic shadow tends to be circular in outline. There are no roentgenologic findings which differentiate hypernephroma from any other form of skeletal carcinomatous metastasis." Dresser³ mentions that in the case of a single metastasis with no signs pointing to kidney involvement, the differentiation between this condition and primary osteogenic sarcoma is practically impossible without the removal of a specimen for microscopic study.

In our present case, the lesion of the right ulna (Fig 6) showed a centrifugal type of bone destruction, as the shell of the bony growth and the tip of the ulna were still visible. In other words, it was of medullary origin. Its proximal portion was almost cystic in appearance, showing trabeculae and a fairly thick shell which was of wavy outline. The distal portion appeared more osteolytic. The lesion was definitely invasive in character. Periosteal reaction was seen along the shaft just proximal to the growth as well as along the distal end of the right radius. Considered apart from the clinical history of the case, the roentgenographic appearance of the lesion was quite suggestive of primary osteogenic sarcoma or giant cell tumor of malignant type.

SUMMARY

(1) A case of adenocarcinoma of the kidney with multiple pulsating skeletal metastases is reported.

(2) Pulsating tumors in the skeletal system should merit thorough urologic investigation, even in the absence of clinical symptoms of a primary renal tumor.

(3) The distribution and roentgenologic interpretation of the osseous lesions are discussed.

REFERENCES

- ¹ Geschickter, C F, and Copeland, M M. Tumors of Bone. Rev. Ed., New York, Am Jour Cancer, 513-523, 1936.
- ² Garceau, E. Tumors of the Kidney. 1st Ed., New York and London, D Appleton & Co., 23-27, 1909.
- ³ Dresser, R. Metastatic Manifestations of Hypernephroma in Bone. Am Jour Roent, 13, 342, 1925.
- ⁴ Judd, E S, and Hand, J R. Hypernephroma. Jour Urol, 22, 10, 1929.
- ⁵ Diez, J, and Michans, J. Metastasis esquelética pulsátil de un tumor de Gerawitz. Bol y trab Soc d cir de Buenos Aires, 20, 601, 1936 (Abst Am Jour Cancer, 33, 612, 1938).
- ⁶ Risley, E H. Skeletal Cancer. Boston Med and Surg Jour, 172, 584, 1915.
- ⁷ Piney, A. Carcinoma of the Bone Marrow. Brit Jour Surg, 10, 235, 1922.
- ⁸ de Massary, E, and Weill, P. Carcinose generalisee, cancer des doigts simulant des troubles trophiques. Bull Soc Med de Hop de Paris, 24, 1456, 1907 (cited by Willis, R A. The Spread of Tumors in the Human Body. 1st Ed., London, J A Churchill, 192-193, 1934).
- ⁹ Nitch. Cited by Gibson and Bloodgood.
- ¹⁰ Hand, J R, and Broders, A C. Carcinoma of the Kidney. Jour Urol, 28, 199, 1932.
- ¹¹ von Bergmann. Verhandlungen des 16 Congressen der Deutschen Gesellschaft f Chir, 1887 (cited by Scudder, C L. The Bone Metastases of Hypernephroma. ANNALS OF SURGERY, 44, 851, 1906).

- ¹² Pool, E H Bone Metastasis in a Case of Hypernephroma ANNALS OF SURGERY, 52, 553, 1910
- ¹³ Sabolotnow, P Zur Lehr von den Nierengeschwulsten suprarenalen Ursprungs Beit z path Anat u z allg Path, 41, 1, 1907
- ¹⁴ Eschner, A A Hypernephroma of the Kidney with Metastases to the Manubrium Sterni, Simulating Aneurysm of the Aorta J A M A, 50, 1787, 1908
- ¹⁵ MacLeod, J A, and Jacobs, W F Hypernephroma of the Sternum Med Rec, 100, 979, 1921
- ¹⁶ Cabot, R C Metastatic Hypernephroma of Sternum New England Jour Med, 203, 533, 1930
- ¹⁷ Crile, G, Jr Pulsating Tumors of the Sternum ANNALS OF SURGERY, 103, 199, 1936
- ¹⁸ Roth, L J, and Davidson, H B Metastatic Pulsating Tumors of the Sternum Secondary to Renal Hypernephroma Jour Urol, 37, 480, 1937
- ¹⁹ Storath, E Ein Fall von Hypernephrommetatase in der Nasenhohle Ztschr f Ohrenh, 69, 157, 1913
- ²⁰ Baetjer, F H, and Waters, C A Injuries and Diseases of the Bone and Joints 1st Ed, Paul B Hoeber, 261, 1921
- ²¹ Gibson, A, and Bloodgood, J C Metastatic Hypernephroma Surg, Gynec and Obstet, 37, 490, 1923

THE DELAYED CLOSURE OF CONTAMINATED WOUNDS *

A PRELIMINARY REPORT

FREDERICK A. COLLIER, M D ,

AND

WILLIAM L. VALK, M D

ANN ARBOR, MICH

FROM THE DEPARTMENT OF SURGERY, UNIVERSITY OF MICHIGAN ANN ARBOR MICH

THE CLOSURE of wounds is a technical procedure common to most surgical operations. The ideal toward which surgeons have striven is immediate closure of wounds, to be followed by uninterrupted healing. The primary closure of clean wounds is usually successful no matter what methods are employed, but perfection has not yet been reached since infection and dehiscence still occur in a small percentage of wounds thus closed, no matter what technical measures have been employed.

Many studies have been and are being made on the factors that influence wound healing. Suture material, the nutrition of the patient, allergic reactions, air-borne infection, and operative methods have all been shown to play a part in causing the occasional catastrophe to wound healing, and proper observance of the facts brought out by these studies has further diminished the untoward results.

All wounds probably are contaminated to some degree, due to exposure to the air and to the impossibility of sterilizing the skin, yet, due to the remarkable protective power of most tissues, relatively few so-called clean operative wounds become infected. When infection does take place, it is generally assumed that there has been an error in technic or that an unusual relationship exists between the bacteria and the tissue.

Not infrequently, an otherwise clean wound may become contaminated during the course of the operation because of conditions met in the tissues at the site of the operation. If frank sepsis is encountered and drainage is indicated, the wound will necessarily become infected along the course of the drain. Occasionally a focus of infection such as the interior of the colon may be encountered during operation, in which case drainage is not indicated, and although it is desirable that the wound in the abdominal wall heal without interruption, infection may develop in it to the detriment of the patient. The handling of wounds thus contaminated is still capable of improvement. A method we have used in handling such wounds recently has been helpful to us and will be described.

Infected wounds have always occurred in the human race. The susceptibility of vertebrates to infection increases as one passes up the evolutionary

* Read before the Fifty-second Annual Meeting of the Southern Surgical Association, Augusta, Ga., December 5, 6, 7, 1939.

scale. This diminution of resistance to infection in the higher vertebrates is paralleled by a progressive loss of the ability to repair tissue damage as compared with the remarkable ability in the lower forms of animal life to regenerate whole limbs and organs.¹

The closure of frankly contaminated wounds such as those associated with open approaches to the gastro-intestinal tract, especially in its lower portions, such as colostomies, cecostomies, and inadvertent openings into the colon and rectum, has never been entirely satisfactory. Although many successful primary closures of such contaminated wounds have been carried out, the incidence of infection in them has always been high, carrying with it a prolonged convalescence and a higher mortality. Examination of our own records showed about a 50 per cent occurrence of serious wound infection in the wounds contaminated through some contact with the interior of the lower gastro-intestinal tract.

It has been customary in such cases to place a drain in the wound to provide a route of exit for the exudate of infection to pass when contamination passed to infection. Occasionally the drain, thus placed, was effective, more often the infection became so extensive as to necessitate the removal of all sutures and eventually necessitate secondary closure when the infection had abated.

In 1917, the French surgeons² developed a method of treating potentially contaminated war wounds, called delayed primary closure. It was applied to all wounds in soft tissue, 15 hours or more old, except those of the scalp, face and hands. The method consisted of the usual careful cleansing of skin and deeper aspects of the wounds, wide débridement, culture of the wound, constant flooding of the wound with Dakin's solution or other antiseptic, and wide packing of the wound with flavine gauze. The patient was then sent to the Base Hospital, marked for delayed primary closure. Within 24 to 48 hours, the bacterial flora of the wound was known, and if streptococci were not present, and if there were less than five colonies per plate, the pack was removed and the wound closed under anesthesia. The method had many advantages in that the Field Hospitals and Dressing Stations were emptied rapidly. The first cultures were available early and infections by the streptococci, which carried the highest morbidity and mortality, could be sorted out and treated more adequately. Finally, the surgeon who closed the wound was able to follow it personally. Fraser,³ in 1918, reported an incidence of 9.7 per cent failure in 41 cases of primary closure as compared with 4.5 per cent failure in 63 cases of delayed primary closure. He also reported 31 bacteriologically negative wounds from 35 contaminated wounds after 48 hours' treatment by delayed primary closure, employing a flavine pack in the wound. In 1918, delayed primary closure of all soft-tissue wounds, excepting those in the scalp, face and hands, was advised by the surgeons of the American Expeditionary Force.⁴ The best results were obtained when the wounds were closed within 50 hours.

The differentiation between delayed primary closure and secondary closure is usually interpreted as one of tissue repair rather than that of time Pool¹⁵ defines delayed primary closure as the approximation of wound edges without excision, while secondary suture is taken to mean that the epidermis has grown inward over the granulations and must be excised and lifted before good approximation and union can be obtained. In late secondary closure, granulation tissue must also be excised.

During the past few months, a method of delayed closure of frankly contaminated wounds has been carried out that has given fewer infections and a much higher incidence of uninterrupted healing than was secured by the primary closure of such wounds with or without drainage. Its employment has been largely confined to wounds contaminated during operation upon the lower bowel. The method is not in any sense unique, since surgeons have, from time immemorial, packed wounds with various substances with the expectation of closing them later, and it has been a common practice to pack wounds contaminated during appendicectomy without even applying sutures.

This method was first employed by us on a patient with a carcinoma of the sigmoid colon. Previous to his entrance to the University Hospital, he had developed acute intestinal obstruction and an operation had been performed to relieve this obstruction. The cecum had been delivered through a right rectus incision and he still presented most of the cecum in this wound when first seen by us. The original incision was badly placed for resection of the lesion in the sigmoid, so an incision was made through the left rectus muscle and the lesion resected and an end-to-end anastomosis made. There was, unfortunately, some contamination of the field during this procedure. The peritoneum was closed with double No. 000 plain catgut and the fascia closed with interrupted sutures of a No. 30 stainless steel wire. It was certain that the wound was contaminated both from proximity to the cecostomy and because of misfortune during the anastomosis. It was decided to pack the subcutaneous tissue with flavine gauze, but to place fine silk sutures to be tied later since it seemed inevitable that infection would occur. Cultures were taken which showed the usual intestinal flora. The next day the pack was removed, cultures again taken, a biopsy secured from the wound and the sutures tied, thus securing approximation of the wound. The wound healed without event. Later the cecum was closed, returned to the abdomen, and the wound associated with this approximated in a similar manner, again with a good result.

Since then we have employed this method of wound closure, under similar circumstances, upon 21 patients, the details of which are shown in Table I. As can be seen, we have secured uninterrupted healing without infection in all except one instance, in which a small abscess containing about 1 cc of pus appeared in the wound, this cleared up rapidly following evacuation of the exudate.

In all cases, the wound has been closed as described, namely, with con-

TABLE I

TWENTY-ONE CASES OF DELAYED CLOSURE OF CONTAMINATED WOUNDS

No	Name	Diagnosis	Operation	Healing
1	A T	P O carcinoma of sigmoid	Closure of colostomy	No infection
2	J M	P O carcinoma of sigmoid	Closure of cecostomy	No infection
3	J M	Carcinoma of sigmoid	Obstructive resection	No infection
4	A L	Carcinoma of sigmoid	Obstructive resection	No infection
5	A L	P O carcinoma of sigmoid	Closure of colostomy	No infection
6	E H	Carcinoma of sigmoid	Obstructive resection	No infection
7	A H	Perf diverticulum	Obstructive resection	Minor infection
8	A H	P O diverticulum	Closure of colostomy	No infection
9	R C	P O carcinoma of rectum	Revision of colostomy	No infection
10	A M	P O carcinoma of rectum	Bilateral herniorrhaphy	No infection
11	L W	Ulcerative colitis	Right colectomy	No infection
12	B W	P O regional ileitis	Closure of colostomy	No infection
13	E K	Fecal incontinence	Closure of colostomy	No infection
14	W K	Perforated appendix	Appendicectomy	No infection
15	L L	Regional ileitis	Exclusion of ileum	No infection
16	W G	Biliary fistula	Closure of fistula	No infection
17	I D	Fecal fistula	Closure of fistula	No infection
18	M M	Ulcerative colitis	Left colectomy	No infection
19	T G	Carcinoma of rectum with perforation	Combined abdominoperineal resection	No infection
20	J S	P O perforated appendix	Excision sinus	No infection
21	M H	P O carcinoma splenic flex	Closure of colostomy	No infection

tinuous sutures of fine catgut in the peritoneum and interrupted sutures of stainless steel wire in the fascia. Various ways of applying the silk sutures to the skin and subcutaneous tissue have been tried but the near-far, figure-of-eight method has been found to be the most satisfactory. The flavine pack need be only large enough to cover the denuded areas and is best applied in two portions, one from each end, to meet in the middle, because they are removed more easily than one long pack. The method is shown in Figures 1 and 2.

The patients complain of very little discomfort at the time of the removal of the pack and the approximation of the wound when tying the sutures. When the pack is removed, it has been a uniform observation that the wounds appear dry and there is a certain stickiness to the surfaces that aids the closure. Microscopic study of sections of the wound edges, at 24 hours, shows an exudate which consists of fibrin, in the meshes of which are polymorphonuclear leukocytes, wandering cells, some necrotic tissue and many young fibroblasts. Several wounds have been left for 48 hours before removal of the pack, and sections of the wound at this time show more fibrin, many more leukocytes and a definite increase in the number of fibroblasts. The characteristic reaction seen in the margins of the wound is shown in the photomicrographs in Figures 3 and 4.

Howes, Sooy and Harvey⁶ have described a "lag-period" in wound healing, during which time the wound has little if any tensile strength. This period lasts from four to five days and corresponds to the stage of exudative reaction

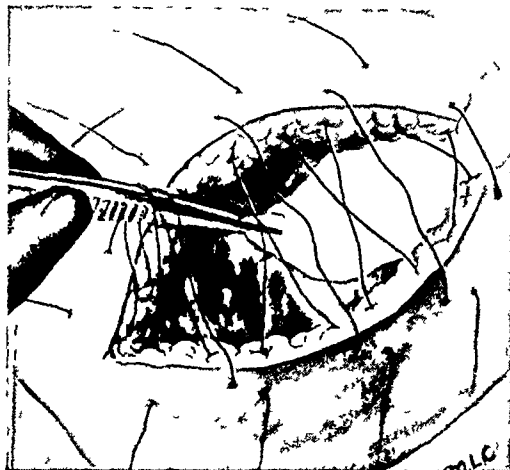


FIG 1—Acriflavine pack being placed in wound

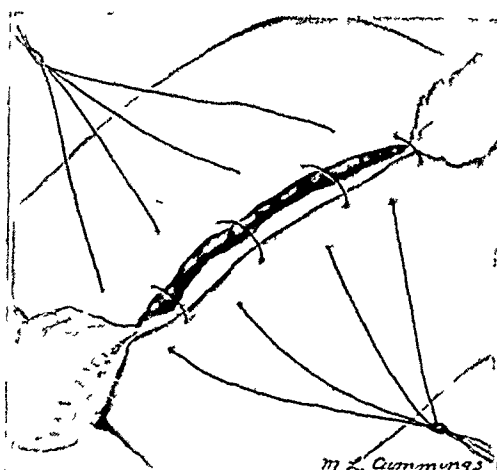


FIG 2—Acriflavine pack in place

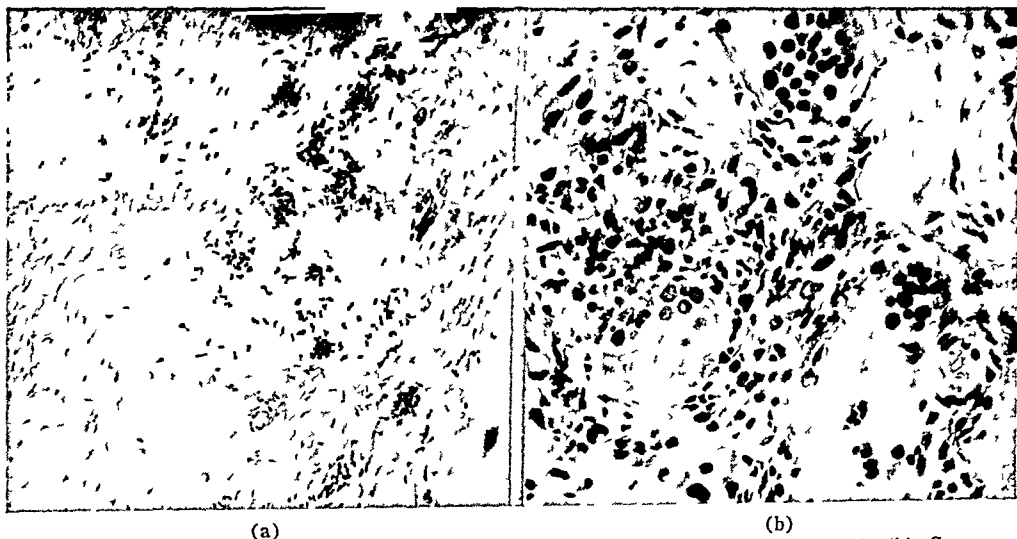


FIG 3—(a) Biopsy of wound 24 hrs p o at time of delayed closure ($\times 185$) (b) Same as above ($\times 750$)

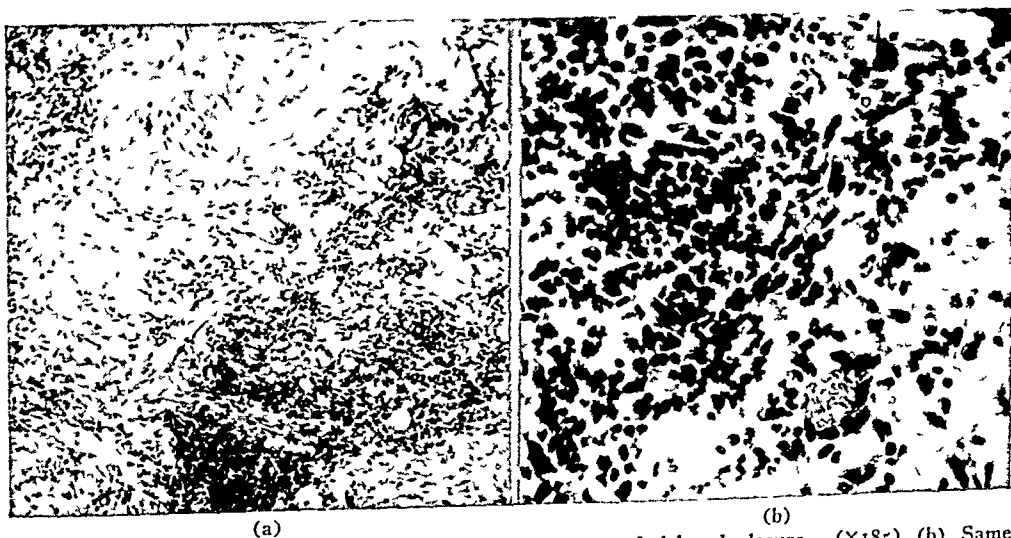


FIG 4—(a) Biopsy of wound surface 48 hrs p o at time of delayed closure ($\times 185$) (b) Same as above ($\times 750$)

in wound healing The critical time for the wound, as far as infection is concerned must occur during the exudative reaction before fibroplasia begins DuMortier⁷ smeared *Staphylococcus aureus haemolyticus* over the suture line of guinea-pig wounds at various time intervals postoperatively, and found that, up to six hours, postoperatively, the wounds were infected in 100 per cent of the cases with many virulent widespread infections of the entire abdominal wall Twenty-four hours postoperatively, 66 per cent of the wounds were infected, 48 hours postoperatively, 56 per cent infections, four days postoperatively, 10 per cent infections, six days postoperatively, no wound infections, after six hours postoperatively, all wound infections were local and without systemic reactions It has been suggested that after coagulation of the fibrin occurs, the resistance of the wound is greatly increased because of the accompanying sealing off of the capillary and lymph spaces, tending to keep infection localized or below the clinical horizon Delayed closure of contaminated wounds, such as described, must, in a similar way, carry the wound through this critical period, probably by aiding coagulation of the fibrin so that when the wound surfaces are brought together a more unfavorable environment is present for the bacteria in the wound

No additional benefit has been noticed from leaving the pack in the wound for two days, and at present we are removing the pack and tying the sutures 24 hours after operation Cultures have been taken from the wound at the termination of the operation in ten cases, all of which showed dominantly *B coli* with fewer *Staphylococcus aureus* and *Streptococcus anhaemolyticus* Cultures were also taken on the same wounds at the expiration of 24 hours, and these were still positive with the same bacterial characteristics Consequently, the packing of the wound apparently has no bactericidal effect, although we cannot state that it may not have a bacteriostatic one

Since the peritoneum and the fascia have been contaminated to the same degree as the skin and subcutaneous tissue and these layers have not shown infection in spite of being closed by sutures, one might assume that they have a higher degree of resistance to infection than has the subcutaneous tissue This observation and clinical experience suggest that infection in wounds of the abdominal wall frequently begin in the subcutaneous tissue and spread to deeper layers from this plane The low resistance of fat to infection is well known It is known that from eight to twelve hours usually elapse before infection supervenes in a contaminated wound, and it is possible that the irritation of the gauze produces an early inflammatory reaction in the subcutaneous tissue that is protective and that inhibits the transition from contamination to infection

Experimental work to determine this point is under way We have neither tried the administration of sulfamidamide to these patients, although it may well be useful in those wounds contaminated by the *Streptococcus haemolyticus*, nor have we tried the local use of antiseptics, including washing with soap and water, as suggested by Jackson,⁸ therefore, we cannot contrast these

methods with the one described. It is obvious that contamination by certain virulent organisms, or by the common organisms, in patients with lowered resistance may give rise to serious infections if contamination occurs. Judging from this limited experience, we believe that delayed closure of wounds of the abdominal wall may be helpful in the occasional case where contamination has occurred either because of the nature of the surgical problem or because of accidents in technique.

SUMMARY

A method of delayed closure of contaminated wounds has been described with a report of 21 consecutive successful wound closures without serious infection.

REFERENCES

- ¹ Arey, L. B. Wound Healing. *Physiol Rev*, 16, 327-407, July, 1936.
- ² Hepburn, H. H. Delayed Primary Suture of Wounds. *Brit Med Jour*, 1, 181-183, February 15, 1919.
- ³ Fraser, F. Suture of Gunshot Wounds. *Brit Jour Surg*, 6, 92-124, July, 1918.
- ⁴ Bleier, E. Delayed Wound Suture. *Am Jour Surg*, 33, 178-182, August, 1919.
- ⁵ Pool, E. H. War Wounds. Primary and Secondary Suture. *J A M A*, 73, 383, August 9, 1919.
- ⁶ Howes, E. L., Sooy, J. W., and Harvey, S. C. Healing of Wounds as Determined by Their Tensile Strength. *J A M A*, 92, 42-45, January 5, 1929.
- ⁷ DuMortier, J. J. Resistance of Healing Wounds to Infection. *Surg, Gynec and Obstet*, 56, 762-766, April, 1933.
- ⁸ Jackson, R. H. A Simple, Efficient Method to Diminish the Incidence of Primary and Secondary Infection in Surgical Wounds. *Surgery*, 6, 3, 398-409, September, 1939.

DISCUSSION —DR DERYL HART (Durham, N. C.) I will restrict my discussion to the paper of Doctor Walters. First, I want to emphasize that we do not consider contaminated air as the only source of wound infections. It assumes a position of major importance only after other sources such as supplies, instruments, and skin have been eliminated or reduced to the minimum. In our own operating rooms we believe that the air contaminated with pathogenic bacteria given off from the respiratory passages of human beings was the greatest source of danger to the open wound until steps were taken to remedy this condition. Since this hazard has to a large extent been removed, we have had a most striking improvement in our results, as indicated not only by reducing the infection rate in clean primary incisions from 4 per cent to less than 1 per cent, but there has been no serious infection in such wounds, and the patients whose wounds did not show signs of suppuration have had much less local and systemic reaction. The postoperative temperature elevations have been lower and of shorter duration.

There are wide variations in the number and type of organisms found in the air, corresponding to similar changes in the nose and throat flora of the occupants of a given area. We rarely have many carriers of the hemolytic streptococcus, but the respiratory tract carriers of the *Staphylococcus aureus* have varied from 15 to 80 per cent of the general population. On the basis of cultures of the air made in other operating rooms over the country we feel that this distribution of staphylococci must be widespread. Our wound infections were caused almost entirely by the hemolytic yellow staphylococcus, a streptococcal operating room infection being almost unknown. This

might be contrasted with the report of Walker from a teaching hospital in Boston where, during an epidemic of streptococcal sore throats, approximately 10 per cent of their operative wounds became infected with the hemolytic streptococcus

During the first six years of the Duke Hospital, before instituting bactericidal radiation in the operating rooms there was a total of 15,557 operations. During this time there were at least seven deaths from infections in clean incisions on the general and neurosurgical services alone: three extrapleural thoracoplasties, primary stage, one extrapleural thoracoplasty, secondary stage, two craniotomies, and one radical mastectomy, all caused by the hemolytic *Staphylococcus aureus*. During the next three years, 10½ months, or up to December 1, 1939, out of a total of 23,213 operations, 1,062 clean, primary operations and 105 clean secondary operations (reopened wounds), on the general, orthopedic, and neurologic surgical services, were performed in a field of bactericidal radiation. Even though most of the larger operative procedures such as thoracoplasties, arthroplasties, bone grafts, laminectomies, craniotomies, ventral herniorrhaphies, etc., were included in these groups, not one of these patients died as a result of, or had his life seriously threatened by, an infection in the wound. During this same period one patient having a craniotomy and decompression performed for an inoperable left cerebral glioma, when bactericidal radiation was not available, died of meningitis caused by the hemolytic *Staphylococcus aureus*.

During the 12 months from November 1, 1938, to November 1, 1939, there were over 600 clean, primary incisions made in a field of bactericidal radiation with only one postoperative wound infection of sufficient note to be diagnosed at the time of the patient's discharge from the hospital. This occurred in a patient having a laminectomy immediately following injury, the operation being performed through skin which showed superficial abrasions, and deeper tissues which were contused and infiltrated with blood. In spite of such a condition of the skin, this infection was thought to be hematogenous since it came on nine days after the operation, and five days after a postoperative pneumonia with an associated septicemia, pyelitis, and cystitis, all caused by the hemolytic *Staphylococcus aureus*. On careful review of each of these records there were five other mild, or questionable, wound infections as follows:

- (1) Herniorrhaphy—stitch abscess. Maximum temperature 99.5° F.
- (2) Craniotomy—stitch abscess.
- (3) Open reduction old fracture dislocation of ankle, lengthening tendon of Achilles. Skin necrosis. Infection limited to denuded and exposed area, joint not involved.
- (4) Arthroplasty hip—vitallium cup inserted, and superficial drains—postoperative hemorrhage. Infection limited to drainage tract, joint not involved—apparently retrograde infection from skin.
- (5) Thoracoplasty, extrapleural—hematoma in incision, drained. Considered not infected by those who dressed it, but a positive growth of *Staphylococcus aureus* was obtained from the draining blood clot. Second stage performed 29 days after first stage.

We feel that by greatly reducing the number of viable pathogenic bacteria in the air about the wound and sterile supplies, we have reduced our postoperative wound infections by over 75 per cent and greatly diminished their severity, at the same time improving wound healing following most of our larger operations.

In regard to the work of Devenish and Miles, it is my opinion that they were dealing with a special condition. Cultures of the skin of one surgeon consistently showed a heavier contamination with a more pathogenic strain of yellow staphylococci than similar cultures taken from the skin of another surgeon and other members of the operating teams. With many punctured gloves, naturally, the surgeon with the more highly contaminated skin had the greater percentage of infected wounds since the hands cannot be completely freed of organisms. When the skin of a patient or his surgeon is known to harbor more virulent yellow staphylococci as indicated by recurring boils, operations of election should be postponed until such a condition can be eliminated.

Whether or not one considers the air to be an important medium for transporting pathogenic bacteria to operative wounds and whether or not one undertakes to remedy the condition, one must not neglect other sources of contamination and must maintain a surgical technic which leaves his wounds in the best condition for the body defenses to handle the bacteria which gain access. Regardless of how aseptic conscious we may be and what measures we may employ, we have not yet attained such ideal conditions that we can operate with assurance that no pathogenic organisms will reach the wound. Fortunately the wound that is in the best condition to handle the bacterial contaminants is also in the most ideal condition for healing.

DR ROY D. McCLURE (Detroit, Mich.) I would like to ask Doctor Coller whether or not he made anaerobic cultures in these wounds. Dr W. A. Altemeier,* of our staff, has been taking both aerobic and anaerobic cultures from cases of peritonitis and wound infection secondary to appendicitis or intestinal surgery. Mixed cultures containing as many as five to seven different species of bacteria were usually obtained by him. The anaerobic organism frequently predominated. He has found the virulence of these bacteria in pure culture to be very low for laboratory animals. Collectively, however, three or more strains have a high degree of synergistic pathogenic action, producing large areas of cellulitis and gangrene when injected subcutaneously.

The treatment of such wounds with zinc peroxide, as advocated by Meleney, has been very successful in our hands, when combined with adequate drainage. Perhaps part of Doctor Coller's success was due to the inhibitory effect of the air upon growth of anaerobic organisms.

DR HUGH A. GAMBLE (Greenville, Miss.) I have been interested in the work of Miles and Meleney ever since their early reports. Their work certainly merits most careful consideration.

There is one feature in regard to infection of wounds which has not been brought out in the discussion this morning, and that is the prominent part played by droplet infection from talking over wounds during an operation.

Some two years ago, a Vienna surgeon reported a series of 1,000 clean operations without a single infection. He laid stress upon the fact that he felt that most infections of clean wounds were due to inadequate masking and unnecessary conversation over the patient. He instituted, in addition to thorough masking, a non-talking technic applicable to everyone in the operating room, using sign language only, and allowing no conversation. To this change he gave full credit for his excellent results.

Shortly after reading this article we instituted a similar regimen in our services. In the period of time since then, my brother and I have performed

* Altemeier, W. A. The Bacterial Flora of Acute Perforated Appendicitis with Peritonitis. A Bacteriologic Study Based upon 100 Cases. ANNALS OF SURGERY, 107, 517-528 April, 1938.

approximately 3,000 clean operations and have had three wound infections in that number. We are convinced that elimination of talking has played a major rôle in the reduction of infections of this character. It is a technic easily learned and consists simply of the use of sign language for instruments, sponges, linen, *etc*

Referring to Doctor Collier's paper upon the method of treatment of wounds, we have advocated a similar procedure both in season and out of season during the last 16 years. First, in 1924, I read a paper before the Mississippi State Medical Association advocating the leaving open of such wounds and also those more virulently infected than the ones Doctor Collier has shown. In potentially infected abdominal wounds, particularly those associated with peritonitis, intra-abdominal abscesses, intestinal obstruction, gangrenous appendices, you are sure to have infections, principally with anaerobic organisms. In the closed wound these infections find an ideal incubator and culture medium and spread in the fascial planes and between the skin and fascia with, at times, most astonishing rapidity and catastrophic results.

Before adopting the open treatment of the potentially infected wound I have seen a number of infections of this character, and reported before the Southern Surgical Association 12 cases of fulminating gangrene of the abdominal wall occurring in the closed or partially closed, potentially infected wounds. Leaving the wound open allows air, which is a specific for this type of infection, to reach all portions of it, and provides for free drainage. Since adopting this plan of treatment for the potentially infected wound, we have had no cases of spreading infection of the abdominal wall.

In the type of case which Doctor Collier reports we feel that he is right in closing it secondarily, but in the type of wound acutely infected with virulent anaerobic organisms, closing the wound after removing the pack is inviting trouble.

As to the manner in which the pack acts in its effect upon the wound it is our opinion that it has (1) A bactericidal effect, (2) it causes a reversal of the flow of lymph, and (3) it limits the spread of infection by the formation of a barrier of inflammatory tissue.

We are definitely of the opinion that the mortality rate in acute intra-abdominal catastrophes such as ruptured appendices, gangrenous cholecystitis, suppurative peritonitis and intestinal obstruction, *etc*, is more often due to anaerobic infection of the soft tissues of the abdominal wall and complicating sequelae than to any intra-abdominal pathology. Since adopting the open treatment of abdominal wounds in such lesions, our mortality rate has been lowered to such an extent that we have largely lost the dread of these conditions.

In a recent review of the cases of generalized diffuse peritonitis secondary to appendicitis, 158 in number, treated, since 1924, by leaving the wounds open, our mortality rate has been under 2 per cent.

DR FRANK K BOLAND (Atlanta, Ga.) I would like to ask Doctor Elkin whether he has ever made cultures of the catgut used in hospitals. We sterilize everything else, but accept catgut as being sterile. Did he ever estimate the difference in cost between silk and catgut? Silk is much cheaper, which is an important item, especially in a large city hospital.

DR FREDERIC W BANCROFT (New York, N. Y.) I think there is another source of contamination of wounds that has not been mentioned. Dr Kingsley Roberts, on my staff, a number of years ago took cultures of the

peritoneal cavity in presumably clean cases. He would take the peritoneal strip up very gently, cauterize it and put in a small applicator and take a culture. These were presumably clean wounds, but he had a 72 per cent culture growth. It is my impression that nothing is sterile. It is true that 60 per cent of these were nonpathogenic organisms. We must, therefore, consider that contamination may be present, and use gentleness and care as well as all the protective measures we know. These were cases of noninfected, clean celiotomies, such as hysterectomies for fibroids, chronic appendices, *etc*

DR WM H PRIOLEAU (Charleston, S. C.) I would like to cite briefly my experience with suture material in thyroid operations. For some years I used fine, plain catgut. In a majority of the cases there was a discharge of serum from the wound. Because of this objectionable feature I changed to the use of fine, black silk. With it the healing was far superior, there being much less induration, and only, occasionally, the drainage of serum. However, in one instance of a severe wound infection, there resulted the extrusion of silk knots over a period of months. This forcibly brought to my attention that the satisfactory use of silk was based upon certain conditions over which I did not have absolute control—such as the operating room technic of rotating internes, some with no previous experience, and student nurses being coached by supervising nurses during the progress of the operation. I next tried fine (No 00-000) chromic catgut which I have been using with satisfaction for several years. It fills a midposition between silk and plain catgut. There is a moderate amount of wound induration, but only seldom the discharge of serum. In one case there was the extrusion of a few knots. In case of infection, it gives no particular trouble. It is to be avoided subcutaneously as it sometimes forms small nodules or sterile abscesses.

I have found great satisfaction in the use of fine alloy steel wire in the repair of herniae, and the closure of celiotomy incisions, particularly in the presence of infection. In the presence of wound infection, it is preferable to silk in that the wire does not become extruded, nor does it act as a focus for sinus formation.

DR W A BRYAN (Nashville, Tenn.) It seems that everybody here agrees that we cannot get rid of bacteria. I think everybody understands that. All we can do is reduce them to as safe a minimum as possible. Doctor Elkins, I think, said that the resident who had 82 cases in the hospital at Atlanta must have done something. I am wondering if his result did not come because he did not do something. That is what I would like to talk about. You know that dead tissue is a much better culture medium than live tissue. We know that traumatized tissue is a much better culture medium than non-traumatized tissue, and we know that tissue in which there is poor circulation or no circulation, although it is still alive, is a better culture medium than where the blood is still circulating. Everybody knows that. Wounds of the face get well readily, wounds of the feet and various other parts of the body do not. Some of us were brought up in the country and when we had to tie a pig we tied him tight so that he would not get loose, you had to tie a bag of oats so that it would not leak. Now we brought that idea into the surgical field and in our overanxiety that the wound should hold we tied the sutures in it good and tight, tight enough to constrict the tissues, and still a little afraid, we tied it still tighter and killed the tissues. This offers a field in which bacteria can grow if they get in.

As between catgut and silk I use one sometimes and sometimes the other. I do not know how much difference there is. I do believe there is a differ-

ence between large ligatures and small ones, and also in masses of material introduced into the tissues. If your assistant gets a wad of fat, or tissue, or ligament inside the forceps and you tie it tight enough it leaves a good site for the culture to grow within the wound. I wonder if one of the differences in favor of silk as opposed to catgut is not the fact that silk will not stand the pull. When you tie with silk you cannot bring it too tightly together because it will break. And, in addition to all that has been done toward reducing the number of bacteria so far as possible and doing whatever you please, I think one of the keynotes is handling of the patient's tissues gently and causing as little trauma as possible. Sutures should approximate tissues, not constrict them.

DR CHARLES C. GREEN (Houston, Tex.) I have a very definite opinion about silk and catgut. " 'Everyone to his own liking,' said the old lady when she kissed the cow." I have lived long enough to see this thing come up and go away and come up again. We have heard the older surgeons tell of the advantages of silk over catgut, then have heard them reverse themselves. You could not make Alton Ochsner use anything but silk, but he has not lived long enough to see it come and go. I think the most convincing argument is to check our own results. I took 100 cases and used silk, and a second 100 cases and used chromic catgut, and in my hands catgut was far superior to silk. You know they tell you "Oh, yes, you do get a sinus or a fistula sometimes." But they do not tell you they last for three or five or six months—that is passed over quickly. I do not think you can deny the fact that the longer a foreign body stays in the tissues the more trouble it causes. Catgut is absorbed much more quickly than silk, consequently it is much less likely to cause infection, with sinus formation, than does silk.

DR RUDOLPH MATAS (New Orleans) I fear that what I am about to say will sound like a very discordant note in this discussion. It is the result of a recent experience in the Military Hospitals of Catalonia during the later months of the so-called Republican regime in Spain. I am referring to the method of treating compound war fractures of the extremities which abounded in all the surgical services and in fact had one entire hospital exclusively devoted to their care. I remained in the Catalonian war zone for over two months while being delayed in the securing of passports for relatives whom I wanted transferred to safety in France.

As a nonpartisan American surgeon, concerned essentially in the medical aspects of the war, speaking the language fluently, with many old friends in the medical profession of the country, I was treated with every courtesy and given free access to all the hospitals and medical centers in the war zone.

I saw many practices, especially in the treatment of war fractures, which, in the light of the present discussion on the importance of atmospheric contamination, were amazing as surgical heresies.

I must say that whatever preconceived notions I had of the treatment of war wounds—derived chiefly from the experience of the World War—were completely upset by what I saw in the Catalonian war zone. The military and civilian hospitals in Barcelona alone, where over 5,000 wounded were under treatment, in Gerona, likewise, crowded with wounded who were being rushed in carloads from the battle front on the Ebro and the Segre, provided an inexhaustible clinic for the study of the most varied war wounds.

The patients were all young men, the flower of the youth of the country—battered, crushed or crippled from the effects of rifle, machine gun, shrapnel, shell and aerial bomb explosions—a fearfully tragic sight to contemplate.

My most interesting experience was at Banolas, near Gerona, where an old monastery had been transformed into a base hospital exclusively devoted to war fractures—except those of the skull with brain injury, which were referred to Neurosurgical Services in other hospitals. I never imagined that one could see such an aggregation of fractures as I saw assembled at Banolas. There were great halls in which several hundred fractured men were treated in separate divisions, classified according to the anatomic seat of the fracture. In one ward devoted exclusively to fractured *femurs*, there were 75 or more patients under treatment, as many, or more, in other divisions for fractured legs, and even more numerous in wards for fractured shoulders, arms and forearms. What an incomparable but lost opportunity for the education and training of a school of young surgeons was the thought that frequently recurred in the presence of this immense mass of traumatized bones and joints!

The fractures of the *femur*, all compound (there were no "simple" fractures in warfare), often multiple, and comminuted, with great lacerations of the soft parts, commanded special attention, not only because of their gravity, but as tests of the efficiency of the revolutionary methods of treatment adopted in the Catalanian hospitals in which antiseptics were totally discarded. The Carrel-Dakin treatment had been tried unsuccessfully and abandoned early in the war. With the great crowding of wounded and inadequate trained help, the rigorous application of the method had proven ineffective, especially since the simplified technic based on the procedures of Winnett Orr (of Lincoln, Nebraska) and Lorenz Bohler, of Vienna, enormously simplified the care of the wounded and yielded better results. The only relic of the World War that remained in the practice of this war was *débridement*, which was the initial procedure in all cases, after hemorrhage and shock had been attended to in the casualty stations and field hospitals. The greatest stress was laid upon the excision of all dead, dying or doubtful tissue and the reduction and setting of the fractures under the fluoroscope or by radiographic control, while the limb was kept in complete extension on a suitable fracture table (Putti's, Bohler's, etc.). While in full extension, under general or spinal anesthesia, the wound was packed with plain sterile gauze so as to reach and drain every recess or pocket where the wound secretions could accumulate. With the fracture set, the wound packed and the limb in full extension, a plaster encasement was applied in hand-molded gauze-plaster sections (not roller bandage) directly in contact with the skin and the wound without any interposed stockinet or padding of any sort, in order to prevent any possible motion under the plaster. The limb, thus thoroughly encased in a close fitting spica, extended from the foot to the waist, including the pelvic girdle. By this procedure, the plaster received the discharges from the wound directly, and soon became soaked with them, but the plaster dried and was not removed for three or more weeks, unless there was evidence of abscess or spreading infection, or gas gangrene, an extremely rare event. After the second week the patients were encouraged to move out of bed with the help of a walking stick. The number of patients with fractured thighs who were seen walking about the grounds in their full-length plaster spicas, with only the help of a walking stick—all seemingly lively and happy—is one of the strange sights that greeted me on entering the hospital grounds.

There seemed to be universal agreement on *débridement*, reduction under mechanical traction and anesthesia, controlled by radiograms or the fluoroscope, with packing of the wound, free drainage into a completely closed and immobilizing plaster encasement, which was allowed to remain, *in situ without change*, until the healing of the wound had advanced sufficiently to become protected by granulation, against secondary infections.

While the fundamental principles of the fracture treatment were the same in all the Catalonian hospitals, there were differences in the methods of reducing and setting them

Dr F Jiménez, the chief at Banolas, a most devoted pupil of Bohler, of Vienna, and thoroughly trained in his methods, resorted to skeletal traction with Kirschner's wire and stirrup tractors, Schmerz's tongs and Steinman's pins—in fact, his wards could have passed easily for a German military clinic except for the patients, who spoke Spanish. As a rule, he resorted to gradual reduction by skeletal traction before packing and encasing the limb in plaster.

Dr Joseph Trueta, chief of the State Military Hospital, in Barcelona, avoided skeletal traction and depended, for reduction, on mechanical extension, availing himself of the open wound and débridement to secure the most perfect apposition of the fragments. After packing, the immobilization of the limb followed with the plaster encasement applied during extension. At first, the wound was packed with vaselined strips of gauze as applied by Orr, but the vaseline gave out and the sterile gauze, alone, was used. There were few cases in which primary suture of the wound had been attempted. All wounds, with few exceptions, that were brought in ten or more hours after the injury were enclosed in the plaster encasement without suture, secondary sutures being applied after the wound had become healthy and filled with granulations.

I had an opportunity to see several plaster encasements removed from arms and thighs after they had been *in situ* for from 15 to 21 days. The stench of the soiled encasement was nauseating. A magma or mush of decomposing pus, wound secretions, including sweat and other matter, covered the surface of the wound under the plaster bandage. But after wiping this off with warm water and soap, and when the packs were removed, I was surprised to see the excellent, healthy, pink, well-granulated appearance of the wounds, coupled with a very satisfactory condition of the patients—no fever, no pain, good appetite, *etc*. This was indeed a revelation which I had not anticipated. Why, no acute streptococcal infections, little or no tetanus, gas gangrene, *etc*, was indeed an extraordinary fact which many theories attempt to explain, but are too long to occupy our attention now. Suffice it to say that when fresh wounds are relieved of all dead or devitalized tissues, they are, when put to complete rest, quite able to take care of themselves without the aid of antiseptics, which (when truly bactericidal) hinder the normal reproduction of the tissue cells and weaken their defenses. At any rate it would seem that a symbiotic existence is possible between the normal tissue cells and the saprophytic bacteria and other pathogenic organisms that gather under cover of a plaster encasement. In fact, if there was one essential for the successful treatment of fractures, it was plaster of paris. By the close of the war, plaster had risen to the level of an apotheosis in surgical esteem.

While in Banolas, Doctor Jiménez kindly gave me a statistical summary of his experience in 6,000 fractures which had been treated under his direction since the beginning of the war, of which 500 were fractures of the femur, which had been treated with a total mortality of 16, or 3.2 per cent¹. There were five amputations—four necessitated by septic infection, and one by gas gangrene which had appeared before admission to the hospital.

Doctor Trueta,² in his little monograph on the treatment of war wounds, was the first to formulate the Catalonian method on the basis of Winnett Orr's teachings, which he practiced early in the war with most satisfactory results.

* Joseph Trueta, M.D. Treatment of War Wounds and Fractures (English version) 1939. Hamilton, Publisher, 90 Great Russell St., W.C., London.

In 1938, he published a record of 605 war fractures, of which 42 were fractures of the femur, without amputations or deaths. In a more recent paper (abstracted in the *Lancet*, London, December 2, 1939) he states that during the war he treated 1,073 fractures of all sorts by the same principles previously described, with less than 0.75 per cent requiring the premature removal of the plaster encasement because of unexpected complications.

Statistical compilations of the experience of the military surgeons attached to General Franco's armies have not yet been collected in sufficient number for general comparison with the Catalonian statistics, but since the majority of the Spanish surgeons have been influenced by Böhler's teachings, the figures of the Victoria Base Hospital, reported by Captain Arguelles Lopez (*Revista Española de Medicina y Cirugía de Guerra*, 1, September, 1938) are comparable to those of Dr Jiménez at Banolas. Thus at Victoria (a Franco hospital) there were 252 fractured femurs, with 20 deaths, or a mortality of 7.9 per cent, and amputations 13, or 5.1 per cent.

This experience, I think, is well worth recording, if only as a contrast to the discussion we are now engaged in. Here, everyone is concerned with keeping germs out of wounds, but despite the great progress accomplished, the best minds are still exercising their wits to devise means and methods to keep them out of the atmosphere. There, at the war front, rude experience imposed by necessity seemed to discount the importance of germs, provided the living tissues were allowed to fight their own battle unencumbered by the bodies of dead or dying tissues, and kept undisturbed and protected in the process of repair and reproduction from tempestuous manipulations and destructive germicidal irrigations by absolute fixation in plaster.

It is true that the smell emitted by these patients while their plaster encasements were ripening was somewhat of a shock to sensitive nostrils. But when I saw them get well, with their wounds healed, I realized that "not all cheese that smells bad, is bad."

DR DANIEL C. ELKIN (Atlanta, Ga., in closing) In answer to Doctor Boland's query as to sterility of the catgut it has been that which meets the requirements laid down by Meleney for sterilization.

DR FREDERICK A. COLLIER (Ann Arbor, Mich., in closing) In answer to Doctor McClure's question whether we took anaerobic cultures or not, I will say that we did not take cultures of this type. The suggestion is an excellent one and it may well be that exposure of the wound to air for 24 hours may play an important part in minimizing or abolishing the growth of anaerobic bacteria.

I am very glad that Doctor Gamble has discussed the paper, as I am sure all of us are indebted to him for the work he has done on the handling of contaminated wounds. For many years, I have followed his advice to leave the wound wide open after severe contamination following operation for acute appendicitis with peritonitis. In the type of wound that I discussed, however, it is highly desirable to preserve an intact abdominal wall if possible and, therefore, we have closed the peritoneum and the fascia, leaving the pack only in the subcutaneous tissues. I wish to emphasize again that we do not feel that this method will be universally successful as it, obviously, will fail in many instances in which the organisms are particularly virulent or in which there is a low tissue resistance. However, we do feel that it may well prevent severe infection in a certain number of wounds that would become infected were they closed in the usual manner.

OPERATIVE AND POSTOPERATIVE INFECTIONS WITH SPECIAL REFERENCE TO AIR-BORNE BACTERIAL CONTAMINATION*

WALTMAN WALTERS, M D , D Sc ,

DIVISION OF SURGERY

AND

THOMAS B MAGATH, M D , Ph D

DIVISION OF CLINICAL PATHOLOGY, SECTION ON PARASITOLOGY

THE MAYO CLINIC, ROCHESTER, MINN

THE FUNDAMENTAL PRINCIPLES underlying the application of bacteriology to surgery were early recognized as basic, therefore, they have undergone very little change since their introduction by von Bergmann¹. Refinements and modernization, however, keep these principles constantly before the operating room personnel and tend to make for more accurate and more careful operative technic in the performance of the necessary surgical procedure with a minimum of trauma and without undue prolongation of the operation.

The contamination of wounds by bacteria, aside from those wounds in which, because of the disease from which the patient suffers, bacteria escape into the tissues either from the gastro-intestinal tract or infected regions, may result by direct introduction of bacteria into the wound. It is obvious that the condition of the wound will have a profound effect on the development of these contaminating agents. In this regard a few simple, yet fundamental, facts should be at once obvious. Tissues whose blood supply has been cut off or which have been devitalized by trauma offer an excellent medium for the development of bacteria, live, normal tissue is by nature resistant. For this reason pieces of tissue which are cut off from a blood supply should be removed. If air spaces are present in wounds, either horizontally or vertically, they offer opportunity for accumulation of serum and exudates which furnish an excellent bacterial medium. Wounds which are dry usually do not permit the development of bacteria as rapidly as wounds which are wet, hence, oozing should always be thoroughly controlled.

Aside from these items, which are entirely in the hands of the surgeon, there is another group of important sources of contamination. First and foremost is the introduction of bacteria into the wound. Meleney,⁹ in reporting a nine-year study of infection in clean operative wounds, listed the possible sources of contamination in the following order: (a) The nose and throat of the operating personnel, (b) the hands of the operating personnel, (c) the skin of the patient, (d) the air of the operating room, and (e) the instruments and materials used in the operation.

The Nose and Throat of the Operating Personnel—In 1930, Walker,¹¹ in studying the incidence of hemolytic streptococcus infections in a hos-

* Read before the Fifty-second Annual Meeting of the Southern Surgical Association, Augusta, Ga., December 5, 6, 7, 1939.

pital in a suburb of Boston, found that in a series of deaths due to hemolytic streptococcus infections following operations on patients who should have had clean wounds, 50 per cent of the nursing personnel of the hospital and three of the six people associated with these operations were carriers of hemolytic streptococci. Following the suspension of operations for a week, the elimination from the operating room of those found to have hemolytic streptococci in the nose or throat and the use of a germ-proof mask worn over both the nose and mouth by most of the personnel, not a single instance of hemolytic streptococcus infection occurred. Another series of wound infections occurred in near-by hospitals, some of these infections were due to hemolytic streptococci. During this epidemic, the results of a study of the customary causes of infection were negative. However, cultures of the nose and mouth of each surgeon, intern and nurse revealed a large number of carriers of hemolytic streptococci. One or more of these carriers had been closely associated with the operation upon the patients infected with the hemolytic streptococci. Walker said "Again, study of the masks revealed that they were woefully inefficient, as far as they could be considered germ-proof. In the absence of other positive evidence, it seemed fair to deduce that this epidemic of streptococcus infection was probably due to streptococcus carriers inefficiently masked." Walker was, therefore, convinced that direct contamination of the wounds occurred from the nose and throat of the operating personnel.

In studying seven different masks he found that none of them could be considered germ-proof. Walker advised inserting between the gauze meshes a piece of thin rubber similar to that used in rubber gloves, a piece of rubber six inches square is incorporated between two layers of gauze ten inches square. In the upper part of the mask he incorporated a piece of aluminum which could be bent to fit the nose of the individual. He stated that the mask had proved to be germ-proof.

The recent contribution of Hart and Schiebel⁷ on contamination of air led these observers to believe that there is a definite correlation between the type and number of organisms found in the air of a given room and in the noses and throats of a group of regular occupants of that room. These authors said that "the number and type of colonies cultured from material taken from the nose and throat seem to parallel more nearly the number and type of colonies cultured from sediment from the air."

The following comment appeared in an editorial on operative sepsis in a recent issue of the British Medical Journal⁸ "Hart's exhaustive studies do not explain how pathogenic staphylococci get into the air of his theatre in spite of all his earlier precautions. These included not only the frequent washing of the room, the provision of filtered air, the wearing of 'large, heavy' masks by all occupants (whether an operation was in progress or not), the exclusion of staphylococcus throat carriers, but even the imposition of silence on all occupants. Any one of the last three of these measures, faithfully carried out, might be expected to prevent contamination of the air from the throats

of the theatre staff, yet, according to Hart, this was the source of infections which continued in spite of adopting all of them "

The Hands of the Operating Personnel—Devenish and Miles,⁴ who studied various sources of contamination of wounds by *Staphylococcus aureus*, placed great emphasis on the rôle played by direct contamination of the wound through needle holes in punctured rubber gloves. These observers found that puncture of a glove was a very common accident. The incidence of puncture in 6,585 patched and unpatched gloves was found to be 24 per cent, while in a second and third series of tests of unpatched gloves worn by surgeons, chief assistants and instrument nurses 14.5 per cent were punctured. The editorial in the British Medical Journal⁵ further stated "The task of Devenish and Miles was made easier by the fact that most of their unexplained sepsis followed operations by a particular surgeon. He was found to be a skin carrier of *Staphylococcus aureus*, and large numbers of these cocci were found in the sweat inside his gloves, they are presumed to have reached operation wounds through small perforations in the glove." It was the opinion of Mr. Devenish and Professor Miles, as well as that expressed by the writer of the editorial, that this was the true explanation of this particular series of wound infections.

The Skin of the Patient—In spite of all of the labor that has been spent to develop a perfect antiseptic it is not yet possible to apply an antiseptic to the skin and sterilize it completely. Many investigations have been carried out, the sum total of which demonstrate conclusively that by no process yet known is it possible to sterilize the skin completely throughout the layers which are cut by the surgeon's knife. Without wishing to enter into the controversy as to which is the best skin antiseptic, it should be evident that at least three properties should be present in the antiseptic. It should kill bacteria in a reasonably short time, it should not be neutralized by the presence of small amounts of serum, fats, soaps, or oils, and its effect should last at least throughout the operation and preferably for several hours after the closure of the wound. It goes without saying that the antiseptic should not be an irritant to the skin. There are a great number of skin antiseptics which kill bacteria in a short time, but on the basis of the stability of these antiseptics in the presence of protein and their duration of action, the choice is greatly limited.

After many experiments it was decided that the antiseptic which most nearly fulfills the requirements at the present time is tincture of merthiolate, this agent, therefore, has been used in preparation of the skin. In order to test the ability of tincture of merthiolate to act for a long period of time, plates which contained 5 per cent of human serum in agar were exposed in a room occupied by several persons. One-half of the surface of the medium in the plates was painted with tincture of merthiolate. The plates were exposed for four hours, then closed for 12 hours, then exposed for two more hours, after which they were incubated. No colonies grew on the side pro-

ected by tincture of merthiolate while numerous colonies appeared on the other side. This indicated that tincture of merthiolate in the presence of at least 5 per cent of serum will retain its activity for many hours. This is an important consideration in the preparation of the skin.

The Instruments and Materials Used in the Operations—In 1932, Dandy³ called attention to the importance of more adequate sterilization in hospitals. He said that in his experience the time generally thought to be satisfactory for sterilization of materials in an autoclave was unsatisfactory and he advocated sterilization in an autoclave for one hour with a constant pressure of not less than 20 pounds. Meleney found that sterilization for 30 to 45 minutes, and prolonging the evacuation time at minus 10 to 15 minutes, was sufficient to kill organisms and spores, whereas prior to his investigation a sterilizing time of 30 minutes at 18 pounds of pressure had been preceded by an evacuation of air just sufficient to reach minus 10 for a few seconds. With this amount of evacuation of air he found that it took an hour and a half to kill test organisms, consistently, in the center of the central drum, and this period of sterilization frequently scorched the materials and softened the gloves. The change in sterilization was followed by inability to obtain growth of organisms from the material autoclaved. It, therefore, is apparent that unless tests are made at frequent intervals to determine the efficacy of the method of sterilization used for autoclaved materials, such materials offer a possible source of wound infection. Mr. Devenish and Professor Miles, in their studies, found that when the skin of a surgeon was infested with *Staphylococcus aureus* the organism would pass through the sleeve of the surgeon's operating gown, if it had been moistened by perspiration or any other cause. Although such source of infection can be indirectly attributed to materials used in the operation, in reality, it is the skin of the staphylococcus carrier. In discussing instruments "sterilized" in antiseptics as a source of infecting organisms, Meleney said that "the sterilization of sharp instruments such as knife blades, scissors and needles, as well as syringes, buttons, silkworm gut, and catgut tubes has been a real problem. Lahey found that soaking for 15 minutes in 50-70 per cent alcohol, which Meleney states was the former method he had used, was entirely inadequate to destroy even the commonest organisms." Meleney said that "now these instruments are either boiled or soaked in pure carbolic acid for 15 minutes and the Bard-Parker germicide is still being used for the sterilization of the catgut tubes which contain the nonboilable variety of gut."

The Air of the Operating Room—Since attention has recently been given to air conditioning it is not peculiar that attention should be directed to the possibility of air-borne infection in the operating room. This is the situation which has always been recognized as a possibility but it is fair to state that even to-day a careful evaluation of the facts has not been made. In recent years, a number of attempts have been made to air-condition operating rooms not only in regard to bacterial content but also in regard to temperature

and moisture. Sufficient evidence has been brought forward to indicate that the bacteria in the nose and throat of the operating team and of the gallery have distinct possibilities in regard to the infection of wounds. It is obligatory upon the individuals to cover the oral and nasal orifices with adequate masks. It is further obvious that the operating room should be stripped of all unnecessary equipment and that it should be kept scrupulously clean. It is not too much to expect that the walls, at least as high as the head, and all fixtures should be washed with a damp cloth at least once a day, and that the floor be sponged with a damp mop. Then if the doors and windows are kept closed one should expect that standard plates of agar medium, set in the room in the absence of occupants, will yield not more than five colonies of bacteria per hour, but as the load of the room is increased the number of colonies on the plate will increase. There are other factors which will increase the bacterial content of the room, particularly the site of the room in relation to currents of air and the velocity of the wind outside. Under conditions of dust storms, thousands of bacterial colonies may develop in a single hour on an agar plate in an operating room, and under these conditions the room should be closed except for emergency operations. It is the general property of bacteria that they settle from the upper to lower strata and eventually to the floor. Bacteria which originate in the nose and throat are not often found above the six-foot level and they filter down to the floor. In order to avoid the falling bacteria, which originate in the gallery, from reaching the operating room some surgeons have had canopies built over the operating table. In our own hospital we have for years had canopies built over the instrument tables, and test plates placed on top of and under the canopy clearly reveal the fact that the canopy offers an enormous protection to the instruments.

Professor Cairns,² in bacteriologic research at Oxford, studied bacterial infection which occurred during intracranial operations and found that *Staphylococcus aureus* accumulated at the average rate of 0.7 colonies per hour on Petri dishes measuring 9 cm. in diameter (about the same size as the portion of brain exposed) during 27 operations, lasting from one and one-half to 10 hours, the average time being four hours.* Two of the 27 patients died of other causes soon after operation. "Of the remainder, all had first-intention wounds and no sepsis, except two. One of these developed osteomyelitis, due to a *Staphylococcus albus* infection of a bone flap, after a ten-hour operation for removal of a large meningioma of the falx, the infection began in the bone, and there was no trace of infection in the meninges, the bone flap had to be sacrificed before the wound finally healed. The other patient, from whom a frontal astrocytoma was removed, had a first-intention wound and no trace of meningeal infection, but fluid accumulating beneath the galea aponeurotica (removed with an aspirating needle and syringe) showed a growth of *Staphylococcus albus*. This patient made a satisfactory recovery."

* Air was pumped into the operating room through a filter of oil and a wet screen of dettol. Dettol was sprayed into the air at intervals during the operation.

Mr Devenish and Professor Miles studied the number of bacteria in the air of a standard operating room under ordinary circumstances and found that on a plate 12 square inches in area, approximately the size of the average exposed operative field, 0.3 colonies of *Staphylococcus aureus* appeared per hour. They said "This is the best available estimate of the continuous risk of infection by *aureus* from the air, though it must vary with the state and staff of the theatre. The area of an operation exposure is usually about 12 sq. in. and the direct settlement on it of one *aureus*-bearing particle every three hours is not an obvious danger." To this they have added, by estimation, the number of these organisms which might have settled on instruments, swabs and gloves and which might be introduced into the wound. They expressed the opinion that the total area of wound and objects introduced into it will not be more than 432 square inches, which is 36 times the area of a plate used for culture. On this basis it is possible that 0.3 times 36, or 11 of these particles, may be introduced into the wound every hour. Mr Devenish and Professor Miles concluded that if each particle consisted of 20 cocci they would be unlikely to settle in one part of the wound and the odds against an inoculum of 20 cocci getting a foothold in relatively healthy tissue must be high. They said that "the rarity with which very small doses of known pathogens can be made to infect susceptible animals, even after passage, makes it unlikely on *a priori* grounds that *aureus* infection would occur readily in such circumstances. We have, however, no direct evidence on the point. Aside from these speculations we have evidence that the air was not responsible, for, whereas its average *aureus*-content remained constant, the suppuration disappeared, although no attempt was made to prevent the access of air bacteria to the operation wounds. In any event, the constancy of infection at the outset of this investigation suggested a source of *aureus* more constant than the air proved to be."

Professor Cairns said "Hart,^{6, 7} (1937 and 1938), who has made a careful study of the bacteriology of operating rooms, has found that the number of bacteria in the atmosphere varies directly with the number of people present, and he has concluded that the bacteria arise from the noses and throats of the people in the theatre, notwithstanding efficient masking. An alternative possibility exists that the bacteria are present beforehand in particles of dust, and that the presence of the people stirs up the dust. There are evidently considerable local variations in the flora of operating theatres, for example, Hart at Duke University, North Carolina, found as many as 78 colonies of *Staphylococcus aureus* per hour on a plate of blood-agar, and most of his infected cases of thoracoplasty were due to this organism (Hart and Gardner, 1937), whereas in London the highest figure we obtained for *Staphylococcus aureus* was 3.6 colonies per hour, and most of the intracranial infections were from other organisms."

Experiments which we have performed in especially constructed rooms indicate that where proper filtration is introduced into the in-coming air the room may be made essentially sterile, only a few colonies of bacteria develop-

ing on plates exposed for 24 hours This type of experimentation and practical application has been extensively used by Reyniers, who has raised mammals under completely sterile conditions His system now in use in the Cradle has demonstrated the low bacterial content of air which can be maintained by proper filtration systems

Recently, attempts have been made to sterilize the air of the room by the use of ultraviolet rays It has been known for some time that certain wave lengths in the ultraviolet series will kill bacteria, but it has never been possible to isolate, completely, light waves which will at the same time produce no erythemic reaction of the eyes and skin For this reason, certain precautions must be taken by the operating force to protect themselves as well as the patient from these rays Wells and Wells,^{12 13} expressed the opinion that the ultraviolet light sterilizing unit should be directed towards the ceiling and that under these conditions no protection of the eyes or skin is necessary They endeavor to sterilize the general air of the room, not the specific operative field, as Hart has attempted to do Hart has suggested that these rays be placed, first, in relation to the field of operation and, second, in certain parts of the room to sterilize the air of the entire room In spite of several analyses of results which have been obtained, it does not yet appear perfectly clear what the function of these rays has been in the series of cases reported Certain experiments which we have performed, as well as those performed by the originators of the lamp, suggest that the rays are effective only under the most limited circumstances For example, Rentschler¹⁰ and his associates, the Westinghouse Electric Company, the originators of the lamp, have stated that the atmospheric dust and grease will coat the glass tubes in which the light is enclosed so quickly, that before each set of experiments is performed the tubes should be wiped with alcohol The penetration of the rays is clearly stated to be extremely shallow, so shallow, indeed, that a layer of muslin, glass, gelatin, serum, or water will prevent the killing of bacteria Any solid object placed between the light and the area desired to be kept sterile will result in a failure, since the rays will not travel around or through the solid object The rays work best in a dry atmosphere, and high moisture content greatly lessens their killing effect In addition, since the humidity of the operating room must be kept high to prevent static sparks, when inflammable or explosive anesthetic gases are used, the rays are forced to work under the most unfavorable circumstances The series of experiments which we have performed, in which the bacteria have been coated with a thin layer of gelatin, have resulted in their almost complete protection This is also true when bacteria are coated with human blood serum In order to demonstrate quick killing of bacteria, the originators of the lamp have found it necessary to conduct their experiments in small, closed boxes, the bacteria held in suspension in water are sprayed into the box where the light is confined in very close quarters Even under these conditions, investigators have not been successful in obtaining absolute sterility As a matter of fact, the experiments show that under the best conditions possible only 90 per cent of

the bacteria are killed. It should be pointed out that these conditions are so artificial that they are never simulated in the operating room, and when one remembers the way the operating field is shadowed by the heads and shoulders of the operating crew it is difficult to see how one can arrange a lamp in such a way that its rays may protect the patient from bacteria which might fall into the wound. Rentschler did not obtain killing of *Staphylococcus aureus* until after 15 minutes exposure at 12 inches from a 30-inch lamp.

Tests which we have performed with the ultraviolet light have indicated that, unless the bacteria are exposed for long periods of time, at close range, to the light, and then without any coating of serum, gelatin, or agar, there is little or no killing to be demonstrated. More or less dry bacteria, exposed in confined regions, are readily killed.

COMMENT—We should like to quote further from the article of Mr Devenish and Professor Miles because it expresses an opinion which at the present time seems to be a reasonable one. "A precise definition of the infection risk from the different sources of *Staphylococcus aureus* is impossible.

Nevertheless, the staphylococcal history of surgeons A and B in the operating theatre strongly suggests that the main danger lay in the *aureus* infestation of A's skin entering the operative wound through puncture holes in his rubber gloves. Wells and Wells (1936, 1938) have, during the past few years, emphasized the importance of the air as a vehicle of pathogenic bacteria, and Hart (1937) has advocated the sterilization of the air in operating theatres by ultraviolet light. Without minimizing the importance of the Wells observations or denying the efficacy of Hart's method of sterilization, it is questionable whether postoperative *Staphylococcus aureus* suppuration is necessarily due to air-borne cocci. Our experience is limited to one surgical unit, but the striking decline of the sepsis-rate, in the face of a continued *aureus* menace in the theatres, suggests that, in other cases, the improvement due to a greater nicety of operative technic may have been wrongly attributed to the elimination of air-borne pathogens. (To this we might add the apparent superiority of one type of suture material or ligatures over another.) Hart, in his latest report (1938), attributes his avoidance of sepsis to 'Meticulous operating room asepsis, development of a delicate atraumatic technic, and the use of the least irritating suture material' besides 'the elimination of air-borne contamination'."

There is no doubt but that the bacterial content of air in an operating room increases with time and the number of persons present, yet no special correlation can be demonstrated between the number of infections and the order of operations performed in any given room. Even yet we do not know the exact source of these bacteria or their significance in regard to wound infection. It is evident, however, that direct introduction of bacteria into a wound by a nonsterile instrument or material, the excretions from noses and mouths of the persons close to the wound, or by sweat from the hands of the operating team through punctures of gloves, are of tremendous significance and an effort should be made first to correct these failures before turning to

the sterilizing of the air of the room. If some effort is indicated in this regard a system of air filtration should be tried but one may not expect to reduce operating room infections greatly until after the first enumerated sources of infection are controlled. Lastly, as has been stated in the British Medical Journal "If Hart is wrong about the source of infection in his cases but right about the beneficial action of his lamp, does this lamp actually kill staphylococci in the wound itself?" This is a matter which it should be fairly easy to investigate.

REFERENCES

- ¹ von Bergmann, Geheimrath. Quoted by Schimmelbusch, C. Die Durchführung der Asepsis in der Klinik des Herrn Geheimrath von Bergmann in Berlin. *Arch f klin Chir*, **42**, 123-171, 1891.
- ² Cairns, Hugh. Bacterial Infection During Intracranial Operations. *Lancet*, **1**, 1193-1198, May 27, 1939.
- ³ Dandy, W. E. The Importance of More Adequate Sterilization Processes in Hospitals. *Bull Am Coll Surg*, **16**, 11-12, March, 1932.
- ⁴ Devenish, E. A., and Miles, A. A. Control of Staphylococcus Aureus in an Operating Theatre. *Lancet*, **1**, 1088-1094, May 13, 1939.
- ⁵ Editorial. Operative Asepsis. *Brit Med Jour*, **2**, 733-734, October 7, 1939.
- ⁶ Hart, Deryl. Sterilization of the Air in the Operating Room by Special Bactericidal Radiant Energy. *Jour Thor Surg*, **6**, 45-81, October, 1936.
- ⁷ Hart, Deryl, and Schiebel, H. M. Rôle of the Respiratory Tract in Contamination of Air, a Comparative Study. *Arch Surg*, **38**, 788-796, April, 1939.
- ⁸ Magath, T. B. Unpublished data.
- ⁹ Meleney, F. L. Infection in Clean Operative Wounds, a Nine-Year Study. *Surg, Gynec, and Obstet*, **60**, 264-276, February 15, 1935.
- ¹⁰ Rentschler. Personal communication.
- ¹¹ Walker, I. J. How Can We Determine the Efficiency of Surgical Mask? *Surg, Gynec, and Obstet*, **50**, 266-270, January, 1930.
- ¹² Wells, W. F., and Wells, Mildred, W. Air-Borne Infection. *J A M A*, **107**, 1698-1703, November 21, 1805-1809, November 28, 1936.
- ¹³ Wells, W. F., and Wells, Mildred W. Measurement of Sanitary Ventilation. *Am J Pub Health*, **28**, 343-350, March, 1938.

WOUND INFECTION*

A COMPARISON OF SILK AND CATGUT SUTURES

DANIEL C ELKIN, M D

ATLANTA, GA

FROM THE DEPARTMENT OF SURGERY, EMORY UNIVERSITY ATLANTA, GA

THE HEALING of a wound is the most important factor in the attainment of good surgery. This is true not only of wounds caused by violence and trauma, but more particularly those made by the surgeon himself. Whipple¹ has stated "A surgeon's percentage of clean-wound healing is not only a measure of asepsis, but it is an index of his entire surgical philosophy—his knowledge of the principles of healing *per primam*—as well as his attitude towards his patient's welfare and towards the improvement of his art and science of surgery." Although these statements are generally accepted as self-evident, it is to be regretted that the appraisal of end-results by a study of wound healing is rarely carried out. Too often this problem is casually cast aside as of no importance or the surgeon salves his conscience by the easy method of exaggerating his own ability by underestimating his percentage of infections.

In many institutions the importance of the wound is minimized by delegating its closure to assistants and members of the house staff. This is excused on the grounds of haste. Disregard of an essential part of an operative procedure is naturally transmitted by the surgeon to his juniors. Furthermore, the responsibility for the care and healing of the wound is shifted or at least divided, and accurate records of individual operators cannot be obtained.

In order to study wound infections, definite criteria must be set up and careful and scrupulous records must be kept. Five years ago such a study was begun at the Emory University Division of the Grady Hospital. In a book devoted entirely to that purpose, all wounds are classified as clean, potentially infected, and infected. The nature of the operation, the name of the operator, and the suture material are noted. At each dressing, and at the time of the patient's dismissal, a notation is made with respect to healing. Every wound which heals *per primam*—without discharge or exudate from the incision or stitch holes—is marked clean. Those showing even the slightest infection are so classified. Serious exudates and hematomata are cultured and if organisms are recovered, these wounds are classed as infected.

The determination of infection and the record of wound healing is made by the resident surgeon and two assistant residents. Since a greater part of the operations are performed by these men, and since keen rivalry exists regarding the character of their work, it is unlikely that an infection will be

* Read at the Fifty-second Annual Meeting of the Southern Surgical Association, Augusta, Ga., December 5, 6, 7, 1939.

overlooked, and it goes without saying that they are eager enough to record the mishaps of their seniors. By this method, and by these criteria, it is easy to analyze the character of the work insofar as infection is concerned. The results, thus compiled and openly discussed, have been the cause of much chagrin. This has led to better care of the wound throughout the operative procedure, an improved technic, and a subsequent response in the reduction of infections.

I had long believed that the number of infections was less in wounds sutured throughout with silk as compared to those in which catgut was employed. This was strikingly proved, when the records of the first year were compiled. At that time, catgut was, and still is, the predominant choice of most of the members of the visiting staff. However, members of the resident staff, who have had ample opportunity to use both materials and observe the results, have, without exception, adopted the silk technic, and have enthusiastically continued its use since leaving the hospital. Moreover, the resident surgeons have assiduously trained their assistants in the use of silk, its contraindications, and in the necessary gentle and careful technic in which it should be employed.

The object of this communication is to present statistical data regarding wound healing, and not for the purpose of discussing the merits and disadvantages of different suture materials. It is generally admitted that the period of exudation is shortened and that fibrioplasia begins earlier in wounds sutured with silk than in those in which catgut is employed. Furthermore, the liquefaction produced in the absorptive process of catgut acts as a fertile culture medium for bacteria. An excellent account of these matters has been published by Howes,² Howes, Sooy and Harvey,³ Whipple¹ and others. It was the belief that infection was less likely to occur with silk than with catgut that led Doctor Halsted⁴ to adopt silk as a suture material in all clean cases. It is only fair to add that his unexcelled records in wound healing were due not alone to the suture material, but to a refined technic based upon complete hemostasis, clean dissection, the avoidance of mass ligatures, undue tension, and meticulous attention to every detail which eliminated tissue trauma.

While the assistants of Doctor Halsted and of Doctor Cushing have for the most part continued to use silk, all insisted that it be employed only under ideal conditions, and have pointed out the possibility of its acting as a nidus of infection. This has led many to abandon its use, although the danger from this source is greatly overestimated. Occasionally when infection occurs a draining sinus will continue until the silk is extruded or removed, but more often healing occurs without removal of the sutures. In five years, there have been only two instances of prolonged drainage from an infected wound, and both healed within six weeks.

Since air-borne bacteria can never be completely eliminated from a wound, it would seem that the technic which tends to limit their growth would be the one of choice, and that silk would, therefore, be preferable even under conditions which were not ideal. Such is the case in the hospital where this

study was made. All the patients were Negroes, and 25 per cent were infected with syphilis. Many were undernourished and anemic. A large percentage of the operations were of an emergency nature. The hospital is old, in a dirty, smoky section of the city, and repairs were frequently being made with resulting dirt and dust. Petri dish cultures, exposed to the air some distance from the operative field, showed 25 implantations of pathogenic organisms after exposure to the air for ten minutes. The rooms were not air-conditioned. The nursing service was entirely by Negro pupils, and a medical student was a member of the operating team in nearly all cases. Ninety per cent of the operations were performed by members of the resident staff, but it is only fair to add that their percentage of infections was less than that of the visiting surgeons. The record and comparison of operations with silk and catgut sutures for the last five years is shown in Table I.

TABLE I
COMPARISON OF OPERATIONS BETWEEN SILK AND CATGUT LIGATURES
Clean Cases

	Silk			Catgut		
	No of Cases	Infected	Per Cent	No of Cases	Infected	Per Cent
1935	81	1	1.2	147	25	17.0
1936	125	4	3.2	154	12	7.8
1937	217	9	4.1	143	6	4.2
1938	452	7	1.5	74	6	8.1
1939	317	4	1.2	77	7	9.1
Totals	1,192	25	2.1	595	56	9.4

It is noted that the percentage was higher in 1937 than in other years. This might be attributed to some controllable cause such as faults in sterilization. However, it was actually due to the high percentage of infections which occurred in the patients of one operator, and the blame must, therefore, be placed in his hands.

It has been stated, and with good reason, that results are frequently better with silk than with catgut because in the employment of the latter large sizes are employed. Furthermore, it has frequently been pointed out that surgeons employing silk are apt to be more careful throughout the whole procedure than when catgut is employed. In this study neither of these factors is applicable. Catgut No. 00 and No. 0 were the sizes generally employed, and the same operators for the most part employed both suture materials.

Noting the marked difference in the wound infections in clean cases, the use of silk has been gradually increased in those wounds which were considered, potentially, but not grossly, infected. These wounds have been studied and compared in a similar manner. They include compound fractures of the skull and long bones, wounds of the heart and chest, wounds of the abdomen without intestinal perforation, gangrenous appendicitis, etc. The comparative results in this group are shown in Table II.

WOUND INFECTION

TABLE II
CASES POTENTIALLY INFECTED
(1935-1939)

No of Cases	Silk		No of Cases	Catgut	
	Infected	Per Cent		Infected	Per Cent
188	15	7.9	312	77	24.7

CONCLUSIONS

- (1) A comparative study of clean wounds sutured with silk and with catgut is given
- (2) Rigid criteria in the determination of infection are necessary
- (3) With silk, infections occurred in 7.9 per cent of the cases, as compared to 24.7 per cent in those where catgut was employed
- (4) In potentially infected cases there was likewise a marked difference—7.9 per cent of the wounds sutured with silk were infected as compared to 24.7 per cent in those cases where catgut was employed

REFERENCES

- ¹ Whipple, Allen O The Use of Silk in the Repair of Clean Wounds ANNALS OF SURGERY, 98, 662, 1933
- ² Howes, Edward L The Strength of Wounds Sutured with Catgut and Silk Surg, Gynec and Obstet, 57, 309, 1933
- ³ Howes, E L, Sooy, J W, and Harvey, S C The Healing of Wounds as Determined by Their Tensile Strength J A M A, 92, 42, 1929
- ⁴ Halsted, W S Surgical Papers The Johns Hopkins Press, 1, 29, 1924

GRADUATE TEACHING OF SURGICAL PATHOLOGY

ARTHUR PURDY STOUT, M D

NEW YORK, N Y

FROM THE SURGICAL PATHOLOGY LABORATORY, COLLEGE OF PHYSICIANS AND SURGEONS COLUMBIA UNIVERSITY,
AND THE DEPARTMENT OF SURGERY, PRESBYTERIAN HOSPITAL, NEW YORK N Y

THE REQUIREMENTS of the various Boards set up to pass upon the fitness of graduates in medicine to become specialists in those fields which have to do with surgery and allied arts, demand a certain amount of training in pathology and more particularly in surgical pathology. In the well-established hospitals, where there are Resident systems for specialty training, a variable amount of time is allotted for this purpose, and graduates of these institutions are usually properly qualified in this respect. But there are not enough such institutions to train the number of men required, and the Resident system does not solve the problem of the many graduates now practicing specialties who wish to become licentiates by qualifying for and passing the examinations of the various Boards. Recently, Graham¹ focused attention upon the lamentable ignorance of surgical pathology displayed by a number of candidates who appeared before the American Board of Surgery. It is safe to conclude, therefore, that there is a very real problem to be met.

The Laboratory of Surgical Pathology at Columbia University has been profoundly affected by this demand. There has always been a certain number of volunteers, not officially connected with our institution, working in the laboratory because they wished to gain greater familiarity with the pathology of surgical diseases, but in recent years the number of such volunteers has increased inordinately so that we are not able to accommodate all of them. Since the effective factor is national, a similar condition must prevail in all parts of the United States. For this reason, I believe it will be in order to report upon the way in which we have organized our facilities to meet the needs of these men.

Before doing this, it will be necessary to point out certain features which characterize the study of surgical pathology. It is the branch of pathology which deals with the study of disease processes as they occur in the living. This has the advantage of permitting the observation of lesions at an early stage, when they may be reversible, but there is also the disadvantage of not allowing the examination in detail of the body as a whole. This lack has to be filled as well as may be by completing the picture with an interpretation of the symptoms, the physical signs and the other laboratory data. Thus, surgical pathology is not a pure science but a branch of clinical medicine. This conception has guided us in planning the activities of those who come to our laboratory to study.

We do not accept volunteers for less than three months but set no other limit to the length of their stay, and a number of men have remained a year

or more. During their sojourn in the laboratory they are required to devote to it a major portion of their time. During 1939, there were 20 workers in the Laboratory of Surgical Pathology in addition to its regular staff. Ten of these were members of the resident staff of the Presbyterian Hospital from the Departments of Surgery, Otolaryngology, Radiology and Pathology, and ten were volunteers.

The work consists basically of a detailed description of the gross and microscopic features of the surgical material and an interpretation of it. This is supervised by the Resident Surgical Pathologist when necessary. The workers are required to familiarize themselves with the clinical aspects of the cases assigned to them and also to keep in touch with all of the cases on the surgical wards by attending the surgical rounds each morning. At the weekly surgical staff meetings, which they must attend, they have an opportunity from time to time of demonstrating the salient features of some instructive specimen. Once a week there is a surgical pathology conference where cases involving difficult diagnostic and therapeutic problems are considered. The clinical history of a case is read, the microscopic preparations are studied, and each participant is asked to express an opinion about the diagnosis and sometimes the treatment. The discussion is concluded with comments by one of the senior surgical pathologists present. These conferences are often attended by other pathologists and radiologists who serve to broaden and increase the interest of the discussions.

Once a month the surgical pathology group holds a joint conference with the radiologists and radiotherapists at which cases of neoplastic and allied diseases involving difficult problems in diagnosis and treatment are jointly considered. The histologic features of each case are projected on a screen and commented upon by one of the senior surgical pathologists.

One day each week the workers attend the Neoplasm Clinic. This is conducted by a group composed of surgeons, radiotherapists and surgical pathologists. The volunteers work up the cases, present them, and then hear the treatment discussed and see the results in follow-up cases.

The third year medical students are given instruction in surgical pathology once a week during a two-hour period. This consists of lectures, the examination and description of gross material and the study of microscopic preparations. The volunteers participate in this instruction by supervising the students' laboratory work.

Finally, those volunteers who demonstrate special aptitude are encouraged to undertake the solution of small problems in surgical pathology.

This program, then, permits the worker to prepare the description of the specimen which will become part of the hospital record, to correlate the lesion with the clinical aspects of the case, and to participate actively in teaching, group discussions, and presentations to the surgical staff. Decidedly, not the least of his privileges is that of enthusiastic and intelligent discussion of current surgical and allied problems with his fellow workers.

The organization of a program for teaching surgical pathology to graduates must of necessity be varied, depending upon the facilities available. However, the writer is convinced that it is essential that it be guided by two principles. First, that the worker shall personally examine and report upon fresh surgical material, and, second, that he shall always correlate it with the clinical features.

REFERENCE

- ¹ Graham, E. A. Report on the American Board of Surgery. ANNALS OF SURGERY, 110, 1115, 1939.

BRIEF COMMUNICATIONS AND CASE REPORTS

TOE TO FINGER TRANSPLANT *

VILRAY P BLAIR, M D ,

AND

LOUIS T BYARS, M D

ST LOUIS, MO

THIS is a clinical series of one case of a toe to finger transplant given as a reintroduction after a six years' absence from our program. The case reported is of a young child who through an accident had lost the distal part of her middle finger of the right hand. The parents' urge that we do something for her was most emphatic.

This is not presented with the idea that it is anything new, but employment of the plan is not likely of common occurrence. It seemed particularly fitted to the needs of the case in hand—restoration of the distal segment of a finger of a young female child. If performed solely for the sake of appearance, such an operation would fall short of its purpose if more than one joint were missing, except possibly on the little finger, where two phalanges might be replaced without attracting attention, using the second toe, but to do this the pedicle of the carrying flap might have to extend up on to the dorsum of the foot. It is also conceivable that the great toe could be substituted for the distal and part of the proximal phalanx of the thumb, this for utility as well as appearance. A partial restoration of the little or the fourth finger might add to the usability of a hand that had lost the three inner fingers, provided either of the two inner metacarpophalangeal joints had been spared to serve as a base for the transplant. If successful, this should facilitate the grip on the handle of a mechanic's tool or a golf club.

In a young subject, the natural difference in appearance between a finger and a toe would be less accentuated by shoe wearing, while the three or four weeks of the unnatural body and limb position would cause less discomfort and be less apt to cause arthritic changes. These could be lessened by a pre-operative practice in the unnatural position.

A girl would be more likely to be distressed by the deformed finger than would a boy or man. The hope that sensation, tactile, heat, cold, *etc.*, will ultimately be restored without having performed direct nerve suture is based on its reappearance in almost all transplanted flaps, usually within nine months. A direct nerve suture would add another step to a somewhat complicated operation. Doctor Byars contrived a laced-on, thin leather jacket in which was incorporated a palmar finger-bar fixed to a tailor's thimble. This is to

* Read before the Fifty-second Annual Meeting of the Southern Surgical Association, Augusta, Ga., December 5, 6, 7, 1939.

be worn constantly over a knitted or kid finger-stall until normal sensation of the transplant is regained, in order to prevent burns or other injuries

Figure 1 shows the hand bound to the foot, but note that the knee was held in extreme flexion and that, also, the forearm and lower half of the arm were bound to the leg and thigh by supposedly nonirritating adhesive tape

Operative Procedure—After making a dorsal slit on the toe, from the center of the second phalanx back to the foot, and removing its proximal and half of the second phalanx, and then making a guillotine disarticulation of the finger stump, the cartilage was scraped from the head of its second phalanx. It also shows that the mobilized distal part of the toe and proximal part of the finger were sutured two-thirds around and to permit this, the original dorsal toe incision had been extended forward, as two arms of a



FIG. 1.—A sketch showing the hand superimposed upon the foot

Y, one to each side of the distal toe joint, thus inclosing an undisturbed dorsal triangle of skin and subcutaneous tissue. This latter was fitted into a dorsal slit made over the end of the finger. Also, about one-third of the transversely cut end of the finger-covering on each side was tacked to the contiguous border of the spread-out distal part of the dorsal toe slit. On the finger, the tendons had been divided at the joint level, and on the toe, 3 Mm proximal to the bone cut off the middle phalanx. The tendons, front and back, were united with three No. 000 silk sutures. Bone fixation was accomplished partly by having these tendon sutures engage also the fringe of joint capsule that had been left surrounding the head of the finger phalanx and on each side this bit of capsule was attached to apposing deep tissues on the toe. The now boneless proximal one-half of the toe thus formed a mobile pedicle long enough to allow the distal half to move dorsally into the axis of the finger. This pedicle was divided four weeks later, after carefully

figuring how much of it was needed for the finger and how much would then remain to cover the site of the toe disarticulation. The latter was closed immediately, but on account of some inflammatory thickening on the finger, we here trusted to the healing to draw together the unsutured bordering

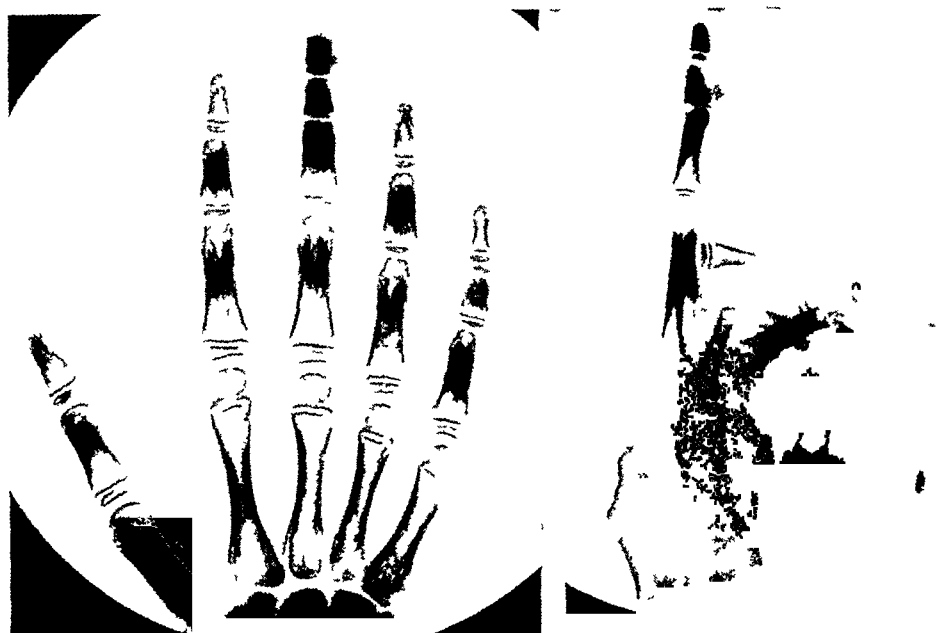


FIG 2—Roentgenogram of the fingers, six weeks after the initial transplantation, showing the inflammatory thickening of the transplant

skin edges. This required about two weeks, but it ultimately made a smooth surface union.

Figure 2 shows roentgenograms, taken approximately six weeks after the initial transplantation, which demonstrate the inflammatory thickening



FIG 3—Photographs (A) showing the preoperative condition, and (B) the cosmetic result 48 days after primary union

of the transplant, but its color and circulation at this time were, apparently, perfectly satisfactory. The only other evident abnormality on the films is that the finger appears to have four phalanges.

Figure 3 shows the preoperative condition and also the result 48 days after primary union.

Figure 4 is a comparison in appearance of the natural with the reconstructed hand



FIG 4—Photograph showing the comparative appearance of the natural with the reconstructed hand

Figure 5 shows that the transplanted joint now remains straight while the fingers are naturally flexed, but she has here already developed a discernible amount of voluntary flexion and extension. We have reason to hope these



FIG 5—Photograph showing the functional result. Note that the transplanted joint remains straight while the fingers are normally flexed

movements will ultimately approach a normal range when, in time, the fine silk sutures loosen that now still fix the already united tendons to the residual fringe of joint capsule that was retained at the site of union

TRANSPLANTATION OF TOE FOR MISSING FINGER*

END-RESULT

HAROLD NEUHOF, M D

NEW YORK, N Y

Case Report—M L, white, female, age 7, came under observation in Mount Sinai Hospital, in July, 1922. Deformities of the fingers of both hands were noted at birth, and also fusion of two toes of the left foot. The hands were useful for ordinary purposes. The right hand presented the chief problem for improvement of the deformity and of function. The thumb, fourth, and fifth fingers were normal. Only the proximal phalanx of the index finger, with its thickened surrounding tissues, was present. The middle finger was totally absent, a short stump of the proximal phalanx, about 1 cm long, projecting beyond the head of the metacarpal bone. The plan was to transplant the second toe of the right foot with part of the metatarsus in the form of a pedicled graft. The metatarsus and adjacent tissues were to be included in order to supply the necessary length. A few days before operation, a plaster of paris mold was prepared to hold the child in position with the right knee flexed and the right arm extended downward in front of the body.

Operation The stump of the missing finger was first prepared. The overlying skin was reflected as a flap, with its base on the ulnar side. The shell of proximal phalanx, found to be of cartilaginous consistency, was exposed and its end freshened. The stumps of the flexor and extensor tendons of the missing finger were exposed and dissected free for a distance of about 2 cm. A wet pack was placed over the hand and dissection of the foot was begun. This consisted in an incision across the web between the first and second toes and extension of the incision over the dorsal and plantar surfaces of the foot. The head of the second metatarsal and the flexor and extensor tendons of the second toe were isolated and were divided about 1.5 cm back of the head of the bone. The tissues on the lateral aspect of the second toe were not disturbed, so that the toe with its adjoining metatarsal bone and tissues swung on a thick pedicle, with undamaged lateral nerve and blood supply. The hand and foot were then brought together by rotating the right leg and bringing the shoulders forward. The problem of adjusting the fingers to the foot was, however, more difficult. The thumb and second finger were placed on the dorsum of the foot, and the fourth and fifth fingers over the sole of the foot. After the hand and foot were placed and held in position, the stump of the finger was approximated to the pedicled toe. A suture of chromic gut was passed through the shell of the phalanx of the missing finger and through the metatarsal bone and tied without tension. The ends of the extensor and flexor tendons of toe and finger were approximated with fine silk. The margin of the skin flap of the finger was sutured to that of the toe. Immobilization was effected by a plaster of paris encasement.

In recovery from the anesthetic the child struggled and the plaster shifted. Some separation of the skin was noted on the third day, and it was necessary to apply adhesive straps to maintain approximation of the skin. The circulation in the pedicled toe remained good.

The detachment of the toe was undertaken 15 days after the first operation. An incision was made across the web between the second and third toes and extended wide

* Presented before the New York Surgical Society, April 26, 1939. Submitted for publication, July 7, 1939.



FIG 1 —Roentgenogram of hand before operation



FIG 2 —Roentgenogram of hand taken several years after operation



FIG 3 —Roentgenogram showing present status. Note the visible phalanges in the graft as well as the increase in size in the stump of the proximal phalanx of the missing finger

TRANSPLANTATION OF TOE FOR FINGER

of the second toe, so that there would be more skin than was necessary. The space in which the dissection was made was cramped and the tendon anastomoses were damaged when the toe (with adjoining metatarsal tissues) was completely detached. It was necessary to remove much of the fat pad on the plantar surface and part of the metatarsus of the transplant, because these structures made too pronounced a prominence for a cosmetic result. The skin margins were trimmed and sutured.

Subsequent Course The circulation remained good in the graft from the outset. The wound healed by primary union for the most part. Sensation was first noted in that part of the graft nearest the finger stump about three weeks after detachment. It advanced in ring-like fashion and sensation was normal about six months after operation.

There were never any symptoms referable to the transplanted toe. About six weeks after operation, it appeared certain that the tendon sutures had not held. Consent for secondary suture of tendons could not be obtained. During the first winter following

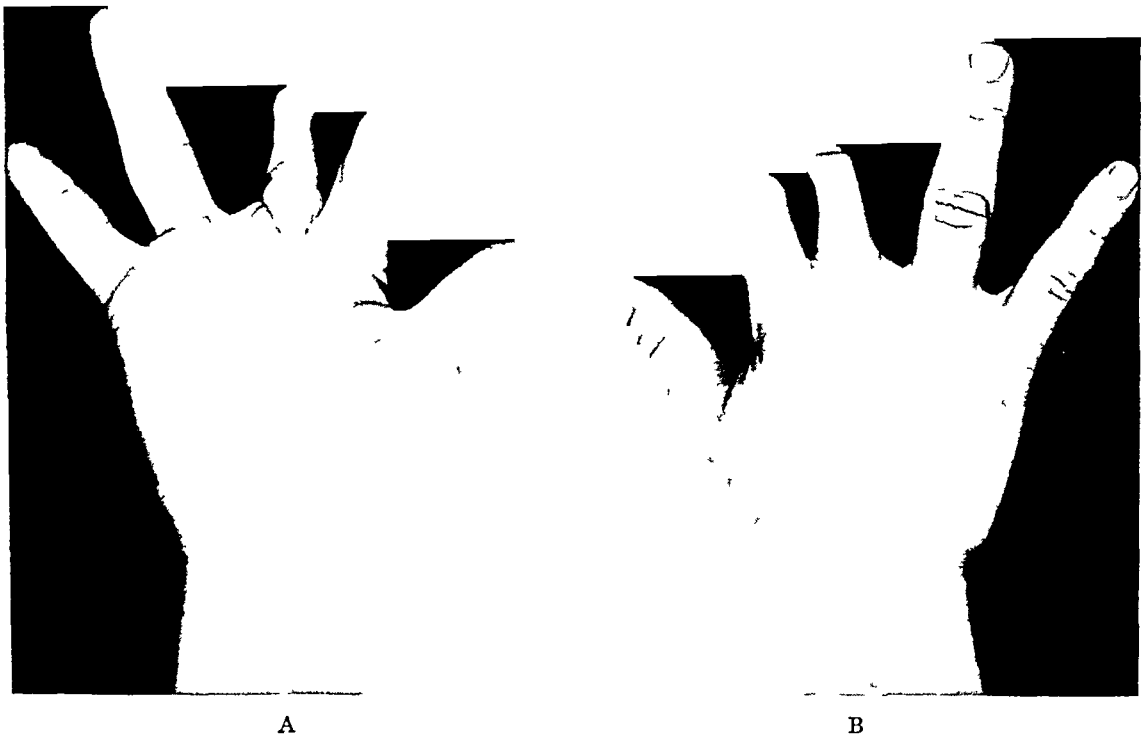


FIG 4—Photographs of transplanted toe at present time. A, Palmar view; B, Dorsal view.

the operation, the transplanted toe was colder and more bluish than the adjoining fingers in cold weather. These manifestations have subsided since that time. The only disturbance in nutrition of the grafted toe was to be noted in the nail. This grew irregularly at first. During the early years it grew more slowly than normal, and the free margin of the nail broke off from time to time.

The function in the transplant is limited to movements transferred to it by the adjoining stump of the finger. Separate motions can be anticipated only if the tendons are sutured or a tendon transplant performed. The roentgenograms show not only survival of the phalanges, but also indubitable evidence of increase in length and thickness. This is most clear in the proximal phalanx of the grafted toe. At no time after operation, in a period of one year during which numerous roentgenograms were taken, was there any evidence of absorption of the phalanges with bone replacement, a phenomenon that had been anticipated. There was a slowly progressive increase in the length and thickness of the transplanted toe until adult life.

End-Result—Seventeen years have elapsed since operation. The end-result is a permanently viable transplant with normal circulation and growth. The cosmetic result is fair. The functional result is *nil*, because the tendons of the graft were not sutured to the tendons of the stump of the finger.

SUPPURATIVE THROMBOPHLEBITIS OF THE FEMORO-ILIAC VEIN WITH BLOOD STREAM INVASION

CASE REPORT

E S VAN DUYN, M D , AND JOHN VAN DUYN, 2ND, M D

SYRACUSE, N Y

•Case Report—H B, male, age 67, was struck by a locomotive, May 8, 1938. He suffered a severe mangle of the left lower leg and was taken to St Joseph Hospital, where a disarticulation at the knee was performed.

Postoperatively, he improved steadily, but the stump was unsatisfactory due to gangrene of the soft tissues covering the end. Six weeks after the first operation, the lower end of the femur was amputated and a new stump constructed, which was drained. A moderate degree of infection developed, but by July 17, 1938, had cleared up considerably and the patient was able to be up and about on crutches.

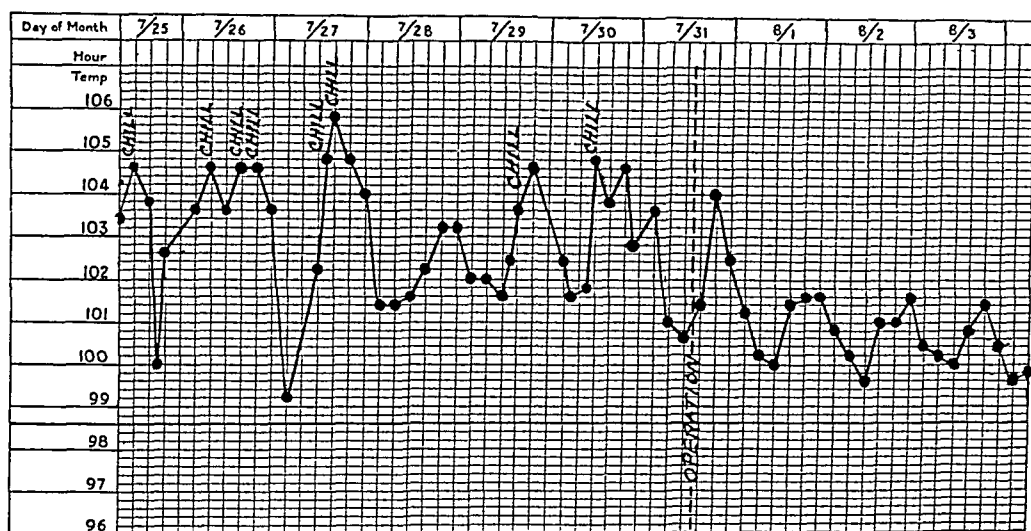


CHART 1—Showing four hour rectal temperature curve from time of first chill to fourth post operative day

Suddenly, on July 25, 1938, after being home eight days, the patient had a severe chill followed by a high temperature (Chart 1). The chills and high temperature continued to recur and were followed by profuse sweats. Within a few days, the stump became markedly swollen with pitting edema, and a blood culture, July 27, 1938, showed a heavy growth of *Staphylococcus aureus*. A diagnosis of suppurative thrombophlebitis of the left femoro-iliac vein with blood stream invasion was made, and scattered râles in the lungs suggested the presence of metastatic foci. On July 31, 1938, six days after the first chill, he was readmitted to the hospital.

Operation—Under spinal anesthesia, a vertical incision was made in the abdomen, extending from the level of the umbilicus downward over the middle of the inguinal ligament. The abdominal cavity was opened low and the peritoneum raised over the region of the left iliac vessels. The left external iliac vein was easily identified and was felt as a firm, noncompressible cord. It was followed proximally to its juncture with the hypogastric branch, just distal to which it abruptly became soft and compressible. It was felt that we were now above the level of the thrombus and at this

point two ligatures of braided silk were applied separately. The thrombotic area of the vein was left intact, being merely overlayed, retroperitoneally, with strips of iodoform gauze which were brought out from the lower end of the wound. The incision was closed in the usual manner after repairing the opening made in the peritoneum.

Subsequent Course—Postoperatively, the temperature rose to 104° F, but was unaccompanied by a chill (Chart 1), and by the next morning the general picture had entirely changed. The patient now appeared convalescent instead of moribund as before the operation. Thereafter, the temperature continued at a low level and the chills did not recur.

Following removal of the drain, there was a moderate amount of purulent discharge for several weeks. The edema of the stump spread upward nearly to the axilla at first, but later receded and eventually disappeared almost entirely. Other postoperative complications included a superficial thrombosis in the other leg from infection at the site of his transfusion, wound in the ankle, also a cystitis, and a persistent arthritis of the right shoulder. In spite of these setbacks the patient's strength gradually returned, and he was finally discharged from the hospital, September 24, 1938, 19 weeks from the date of the accident.

COMMENT—Thrombophlebitis of the infectious and suppurative types constitutes only about 3 per cent of the thrombophlebitides.¹ There is, however, a very high mortality because of the frequency of septicemia and metastatic foci. This high mortality, as recently shown by Rosenow and Brown,² varies directly with the inability of the surgeon to check blood stream invasion from the septic focus.

The idea of trying to stop the spread of infection from a diseased vein into the general circulation apparently originated with John Hunter,³ who, in 1793, advised that a "compress . . . be put upon that part of the vein just above the suppuration." In 1865, Henry Lee⁴ applied this principle and used a ligature for the first time in two of four cases.

In 1878, Kraussold⁵ reported a case of femoral suppurative thrombophlebitis, successfully treated. The patient, a male, age 29, had had an amputation through the condyles of the left femur. Four days later, a severe chill and high temperature developed and the stump was explored. The femoral vein was found to contain a purulent thrombus and was ligated at the level of the inguinal ligament.

In 1884, Zaufal⁶ tied off the internal jugular vein in an instance of lateral sinus thrombophlebitis following suppurative otitis media, and, in 1900, Viereck⁷ showed statistically the value of this treatment. In 1902, Trendelenburg⁸ reported ligations of the ovarian and deep pelvic veins in puerperal sepsis, in 1909, Wilms⁹ ligated the ileocolic angle radicles of the portal vein in appendicitis, and, in 1912, Bullock¹⁰ ligated the facial veins in a case with a carbuncle of the upper lip.

The femoro-iliac vein is a frequent site of thrombosis, but only very rarely is the clot infected.¹¹ When infection does take place it may be hematogenic,^{12, 13, 14} but is usually due to direct extension from a septic focus as in the present case.^{15, 16, 17}

The diagnosis of suppurative thrombophlebitis with blood stream invasion

is easily made, as a rule, by the recurrences of severe chills and high temperatures. Often chills are absent, however, and the temperature curve may not be typical.¹⁸ Edema, of course, helps to locate the area involved. Blood cultures are said to be usually negative.^{18, 19}

Some cases undoubtedly subside without surgical interference, but just how long a case may be treated expectantly cannot be told in advance. Probably a positive blood culture should stimulate active intervention, though waiting for the report might cause serious loss of time. Above all, it should be emphasized, that as long as the patient lives, even though a week or more may have elapsed since the first chill, operation may still offer a good chance of recovery.

SUMMARY

A case of thrombophlebitis of the femoro-iliac vein secondary to amputation of the femur is reported. Simple ligation of the iliac vein was followed by rapid, marked improvement and eventual recovery. It is concluded that in this type of case, even though the patient may appear *in extremis*, operation is indicated.

REFERENCES

- ¹ Barker, N. W. General Classification of Diseases of Veins and Clinical Types of Thrombophlebitis. Proc. Staff Meet., Mayo Clin., 9, 191, March 28, 1934.
- ² Rosenow, E. C., Jr., and Brown, A. E. Septicemia. A Review of Cases, 1934-1936 Inclusive. Proc. Staff Meet., Mayo Clin., 13, 89, February 9, 1938.
- ³ Hunter, John. Observations on the Inflammation of the Internal Coats of Veins. Transactions of a Society for the Improvement of Medical and Chirurgical Knowledge, Printed for J. Johnson, No. 72 St. Paul's Church Yard, London, Chap. 2, p. 29, 1793.
- ⁴ Lee, Henry. The Surgical Treatment of Certain Cases of Acute Inflammation of Veins. Med. Times and Gaz., 1, 530, 1865.
- ⁵ Kraussold, H. Über eine operative Methode zur Bekämpfung beginnender Pyämie. Arch. f. klin. chir., 22, 965, 1878.
- ⁶ Zaufal. Prager med. Wchnschr., 9, 474, November 26, 1884.
- ⁷ Viereck. Die Unterbindung der Vena Jugularis bei der Thrombose des Sinus transversus. Verhandl. d. deutsch. otol. gesellsch., 9, 77, 1900.
- ⁸ Trendelenburg, F. Über die chirurgische Behandlung der puerperalen Pyämie. München med. Wchnschr., 49, 513, April, 1902.
- ⁹ Wilms. Venenunterbindung bei eitriger Pfortaderthrombose nach Appendicitis. Zentralbl. f. Chir., 36, 1041, 1909.
- ¹⁰ Bullock, W. O. Carbuncle of the Upper Lip with Special Reference to the Prevention of Cavernous Sinus Thrombosis. Surg., Gynec., and Obst., 14, 156, February, 1912.
- ¹¹ Homans, J. Venous Thrombosis in the Lower Limbs. Its Relation to Pulmonary Embolism. Am. Jour. Surg., 38, 316, November, 1937.
- ¹² Santrucek, K. Die eitrige Thrombophlebitis und ihre Behandlung (abstr. Case 2). Zentralbl. f. Chir., 47, 984, August 7, 1920.
- ¹³ Rosenstein, P. Die Phlebektomie (operative Ausschaltung der fortschreitender Thrombophlebitis) (Case 3). Arch. f. klin. Chir., 109, 394, 1917-1918.

- ¹⁴ Pool, E H, and McGowan, F J Septic Thrombophlebitis of Femoral Vein, Operative Treatment with Report of Case Arch Surg, 8, 763, May, 1924
- ¹⁵ See reference ¹³ (Cases 1, 2, and 4)
- ¹⁶ Rost Über Venenunterbindung wegen Pyämie bei Extremitätenverletzungen München med Wchnschr, 63, 573, April 18, 1916
- ¹⁷ von Rehren, W Über einem Fall von geheilter Extremitätenpyämie durch Unterbindung der vena iliaca communis sinistra Zentralbl f Chir, 58, 1426, June 6, 1931
- ¹⁸ Neuhof, H The Diagnosis and Operative Control of Acute Pyogenic Phlebitis Complicated by General Septic Invasion ANNALS OF SURGERY, 97, 808, June, 1933
- ¹⁹ Ochsner, A Thrombophlebitis Practice of Surgery, Dean Lewis, W F Prior Company, Vol 12, Chap 5, p 26

CONGENITAL, PEDUNCULATED PSEUDOPAPILLOMA OF ANUS

CASE REPORT

WARREN W GREEN, M D

TOLEDO, OHIO

MALDEVELOPMENT of the proctodeum and distortion of the perineal raphe are among the more common types of congenital anoirectal deformities. Such variations from the normal have appeared in eight (66 per cent) of our 12



FIG 1 —Photograph showing the thickened perineal raphe merging with the base of the pedicle

cases of anorectal malformations. In our group, this type of deformity was not limited to those cases where the occlusion was due to a simple imperforate anus (Group III, Ball,¹ Group II, Berman,² Ladd and Gross³), but occurred in some of the other classifications as well. Although improper development of the proctodeum and perineal raphe is not an unusual deformity, it is rare for such a malformation to manifest itself as a pedunculated growth. A care-

ful search of the recent literature fails to reveal any description or reference to the type of anomaly presented in this report. Because of the simplicity of the surgical measures necessary for correction as well as the lack of functional impairment, only a brief resumé of this case is given.

Case Report—This infant was seen, November 1, 1937, in consultation with Dr Rollin Kuebbeler, who had delivered the child five days previously. At that time he noted the presence of the pedunculated growth which in no way interfered with normal anal function. Examination revealed a patent anal orifice of normal dimensions. The median raphe was thickened, extending from the base of the scrotum across the perineum to the anterior aspect of the anus. At that point, the thickened epidermis veered to the left and at the lateral border was continuous with the pedicle of the tumor. The pedicle was about 4 cm long and the ovoid tumor measured 3×4 cm (Fig 1). Both were covered by what appeared, grossly, to be normal epithelium. Since no associated malformation was present in the anal area or elsewhere, we advised surgical removal of the growth. Doctor Kuebbeler, after infiltrating the base with 0.5 per cent procaine, ligated the pedicle at the left lateral anal margin and excised the tumor. Healing progressed in a normal manner and the deformity was satisfactorily corrected.

FIG 2

FIG 3

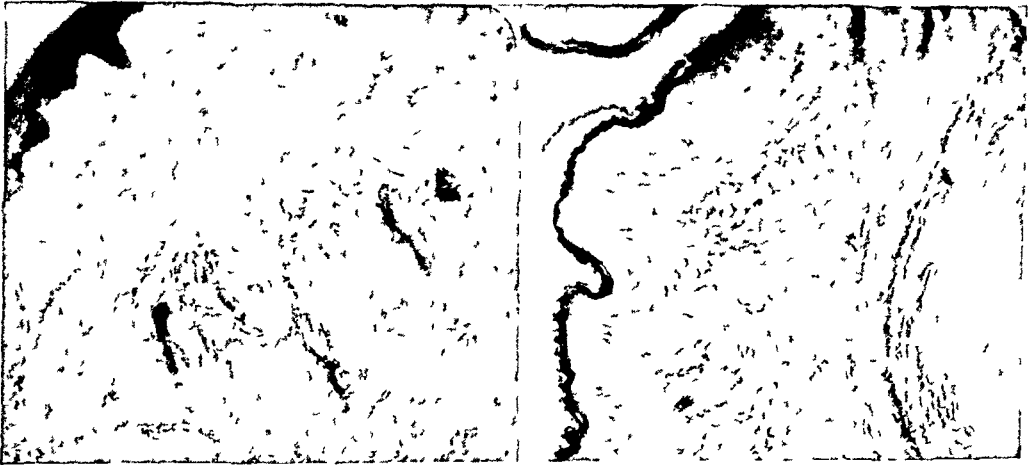


FIG 2—Photomicrograph showing normal structure of skin, subcutaneous, connective and fatty tissues. A few hair follicles and sebaceous gland ducts are present (×100).
FIG 3—Photomicrograph showing a large nerve running through the pedicle (×100).

Sections from the tumor were examined by Dr Thomas L Ramsey, Toledo, Ohio, and Dr Carl V Weller, Ann Arbor, Mich. A summary of their reports states: The diagnosis is that of a congenital, pedunculated pseudopapilloma with fibrolipomatous structure and with a definite well-formed epidermis (T L Ramsey). The specimen is not a true neoplasm but a developmental anomaly consisting of a pedunculated mass of adipose tissue covered with a fairly typical corium and epidermis (Figs 2 and 3) (Carl V Weller).

Sir Arthur Keith⁴ said: "Surgeons are apt to regard embryology as a subject which has little direct bearing on their art. The opposite is the case, that all the changes which bring about the development of the body are instances of superb surgery. Parts are perfectly opposed and, as a rule, exact and orderly union occurs in a manner in which surgeons may dream of but can hardly hope to attain in practice." Thus, the congenital origin of this

growth can best be understood from a brief résumé of the embryology of the anus and perineum. Shortly after the third week of embryonal life the proctodeum invaginates to form the site of the future anus. This ectodermal depression deepens and approaches the descending termination of the blind gut. As these near each other, the intervening mesoblast is obliterated in such a manner that the resulting septum is formed by the entodermal wall of the rectum and the ectodermal epithelium of the proctodeum. This membrane is absorbed and, at about the eighth week, there is normal communication between the anus and rectum. During the second month, the urogenital septum extends to the surface to form the perineal body and, after the beginning of the third month, the outer genital folds coalesce to form the perineal raphe. According to Keith, it is because of the late period of union that so distinct a raphe or scar is left along this line of fusion. Although the cause of these defects is unknown, he offers the interesting hypothesis that the factors producing this scar are of the same order as those preventing the union of ordinary wounds.

Upon reviewing this embryologic process, it is found that failure in the normal development of this area may result in (1) The persistence of a partial or complete membrane in the anal canal, (2) a superficial band of skin partially or completely obstructing the anal orifice, or (3) an unbroken and thickened median raphe covering the outlet. It is a matter of conjecture whether the deformity under discussion had its origin in improper proctodeal development or in a variation from normal of the perineal raphe. The salient points about this anomaly are (1) The presence of a patent anal orifice of normal dimensions, (2) an unusually thickened perineal raphe extending from the scrotum to the anus, and (3) a pedunculated tumor arising from the anal margin and apparently continuous with the raphe. By interpreting these factors from the embryologic standpoint, we feel justified in assuming that the proctodeum developed in a normal manner except for the persistence of the deformed raphe. This latter, instead of remaining in the midline to partially obliterate the anal orifice, deviated to the left to form a pedunculated tumor. Upon this basis, we may conclude that the anomaly under discussion is one of the more common congenital anorectal deformities which has assumed a bizarre and unusual form.

REFERENCES

- ¹ Ball, Sir Chas. B. *The Rectum*. Oxford Medical Publications, New York, 1910.
- ² Berman, J. K. *Congenital Abnormalities of the Rectum and Anus*. Surg., Gynec., & Obst., 66, 11, 1938.
- ³ Ladd, W. E., and Gross, R. E. *Congenital Malformations of the Anus and Rectum*. Amer. Jour. Surg., 23, 167, 1934.
- ⁴ Keith, Sir Arthur. *Malformations of the Perineum* (Hunterian Lecture). Brit. Med. Jour., 1, 489, 1932.

ENTEROGENOUS CYST

OBSERVATION OF AN UNUSUAL PHYSICAL SIGN

CHARLES E REA, M D

MINNEAPOLIS, MINN

FROM THE DEPARTMENT OF SURGERY, UNIVERSITY OF MINNESOTA MEDICAL SCHOOL, MINNEAPOLIS, MINN

THE FOLLOWING CASE is reported not only because of the rarity of the condition, but also because of the observation of an unusual physical sign on examination of the patient

Case Report—University Hosp No 652337 S B, white, female, age two, was admitted to the University of Minnesota Hospital September 21, 1936 The mother noticed that when the patient was five or six weeks old, the baby's abdomen was more rigid or "tight" on the right side When the patient was one year old, the mother felt a mass in the right side of the child's abdomen This mass had gradually increased in size until six months before admission Five weeks before coming to the hospital, the patient began to complain of pain at times in the region of the umbilicus

The past and family histories were essentially negative except for occasional attacks of tonsillitis The child's appetite was good There was no history of intestinal colic, bloody stools, diarrhea or constipation Cardiorespiratory and genito-urinary histories revealed nothing of note

Physical Examination—Negative except for a large tumor in the right lower quadrant of the abdomen This mass was round, movable, not tender, and was apparent on inspection (Figs 1 and 2) and moved on respiration It was dull on percussion No borborygmi were heard on auscultating the abdomen Most interesting of all, however, was a finding first observed by Dr W T Peyton of the Department of Surgery, namely, the mass seemed to have contractile properties, as at times its consistency would change from soft to hard and then become soft again The liver and spleen were not palpable Rectal examination revealed a mass which could be pushed into the pelvis, but which was extrinsic to the rectum

Laboratory examination of the blood and urine was negative Wassermann reaction was negative Roentgenologic examination of the chest and intravenous urograms were normal A barium enema revealed a mass on the right side of the abdomen displacing the bowel to the left and posteriorly There was no roentgenologic evidence of an intra-abdominal hernia *Clinical Diagnosis* Mesenteric or omental cyst, or possible intra-abdominal hernia

Operation—September 29, 1936 Under ethylene and ether anesthesia, the abdomen was opened through a right midrectus incision A large cyst was seen in the right lower quadrant The mass could not be delivered out of the abdominal incision It was about four and one-half inches in diameter, thick-walled, and light in color Large blood vessels coursed over its surface At this time it was difficult to determine the exact connections between the cyst and the intestine A needle was inserted into the tumor and approximately 200 cc of mucoid, grayish, transparent fluid was aspirated It was then possible to lift up the entire mass and deliver it through the abdominal incision (Fig 3) The cyst was in the angle between the cecum and terminal ileum, and the central portion of the attachment seemed to be at the superior angle between the ileum and cecum On attempting enucleation, it was found to be intimately adherent to the wall of the ileum

Submitted for publication February 17, 1939

ENTEROGENOUS CYST

The cyst was opened and the inner lining dissected out of the thick-walled sac. The inner lining was granular and about 1 Mm in thickness. The outer portion of the wall was 3.5 Mm thick and had the appearance of muscular fibers. After the entire lining

FIG 1



FIG 2



FIGS 1 and 2—Front and side views of the patient's abdomen showing the tumor mass on the right side

was removed from the sac, the major portion of the outer wall was then excised and the adherent portions sutured together to make a much smaller closed space. The appendix

was normal. The terminal one and one-half inches of the ileum were dilated. The cecum was not dilated nor was its muscular wall thickened.

The impression at operation was that this was an enterogenous cyst arising from the wall of the terminal ileum.

Examination of the fluid aspirated from the cyst revealed it to be sterile. Specific gravity 1.010, containing 1,300 white blood cells. Sugar 54.5 mg per cent, protein 22.6 mg per cent. There was no mucus.

Pathologic Examination—*Gross*. The cyst measured 8x10 cm. The wall was thick and contained muscle. The inner lining was smooth, there were no papillary ingrowths. *Microscopically* (Path No. HO-36-3190), a smooth-walled cyst was found, lined by a



FIG 3—Enterogenous cyst at operation

single layer of epithelium. In the deeper layer there were glandular structures lined by the same type of epithelium. There was fibrous and muscular tissue in the outer layers of the wall (Figs 4 and 5). *Pathologic Diagnosis*. Enterogenous cyst arising from the terminal ileum.

The patient made an uneventful convalescence and was discharged, October 9, 1936. Two years later she was in excellent health.

Discussion—It is not the purpose of this paper to discuss in detail the etiology, incidence, pathogenesis, etc., of enterogenous cysts. Excellent reviews have been given by Evans,³ Hughes-Jones,¹ and others. Suffice it to say that two theories have been advanced regarding the etiology of these cysts: (1) That they arise from diverticula of the intestine of the embryo, and (2) that the epithelium becomes detached from the embryonic intestine at a very early age and develops into a cyst. The cyst may occur anywhere along

the small or large bowel, however, of 55 cases collected by Hughes-Jones, 31 occurred in the region of the cecum and last four inches of the ileum

With regard to the position of the cyst in relation to the wall of the intestine, it has been noted that the tumors in the jejunum and upper ileum are chiefly mesenteric in distribution, while in the ileocecal region, their incidence is greatest in the submucous and muscular layers. The tumors frequently show symptoms within the first years of life. They also occur more frequently in the female than in the male (3, 2). The clinical manifestations of



FIG 4—Photomicrograph of section of the inner lining of the cyst. Note the epithelial lining and glandular structures in the deeper layer. (X65)



FIG 5—Photomicrograph of section of outer wall of the cyst consisting of the muscular and fibrous tissue. (X200)

this condition are of special interest. According to the available literature, no case of enterogenous cyst has been diagnosed before operation. Most of these tumors give signs of intestinal obstruction. Of 34 cases collected from the literature by Hughes-Jones, the clinical picture of intestinal obstruction was present in 14, intussusception in six and volvulus in three. In some instances, the patient was thought to be suffering from appendicitis.

Our case is, apparently, the only one to have been reported in which contraction of the cyst was noted on physical examination. Millar and Robertson⁴ describe a case of an enterocystoma, in which they believe the symptoms of vomiting and abdominal pain were due to temporary strong peristalsis of the patient's intestine which was shared by the cystoma. The fact that there may

be contraction and relaxation of the cyst, as observed in our case, lends credence to this view

Treatment of this tumor consists in (a) enucleation, (b) excision of the bowel containing the cyst, (c) marsupialization, and (d) evacuation. Of these, enucleation is the procedure of choice. Hughes-Jones collected nine cases in which enucleation was attempted, five were successful and four were not. Miller¹⁵ recorded ten instances of enucleation of cysts without a death, while he estimated the mortality from resection was 60 per cent. Marsupialization and evacuation of the cyst have been tried too few times to be evaluated, but theoretically these procedures would seem less desirable than removal of the tumor.

SUMMARY

A case of an enterogenous cyst arising from the terminal ileum in a female, age two, is reported. Contraction and relaxation of the cyst was noted on physical examination. Brief mention has been made of the etiology, incidence, clinical manifestations and treatment of this condition.

BIBLIOGRAPHY

- ¹ Hughes-Jones, W E A. Enterogenous Cysts. *Brit Jour Surg*, 22, 134, 1934-1935
- ² Edwards, H. Congenital Diverticula of the Intestine, With the Report of a Case Exhibiting Heterotopia. *Brit Jour Surg*, 17, 7, 1929-1930
- ³ Evans, A. Developmental Enterogenous Cysts and Diverticula. *Brit Jour Surg*, 17, 34, 1929-1930
- ⁴ Millar, R E, and Robertson, G. Enterocystoma. *Brit Jour Surg*, 17, 373, 1929-1930
- ⁵ Lewis, F T, and Thyng, F W. The Regular Occurrence of Intestinal Diverticula in Embryos of the Pig, Rabbit and Man. *Amer Jour Anat*, 7, 705, 1907-1908
- ⁶ Horn, L J. A Retroperitoneal Enterogenous Cyst. *Brit Jour Surg*, 23, 676, 1935-1936
- ⁷ Strode, J E, and Ferinel, E A. Enterocyst. *Surg, Gynec and Obstet*, 37, 781, 1923
- ⁸ Shallow, T A. Entero-Mesenteric Cysts. *ANNALS OF SURGERY*, 81, 795, 1925
- ⁹ Drennen, E. Ileocecal Cysts. *Arch Surg*, 22, 106, 1931
- ¹⁰ Aitken, R Y L. Cyst of the Ileum. *Brit Jour Surg*, 18, 521, 1930-1931
- ¹¹ Black, R A, and Benjamin, E L. Enterogenous Abnormalities. *Amer Jour Dis Child*, 51, 1126, 1936
- ¹² Sherwin, B. Enterogenous Cysts. *Amer Jour Surg*, 40, 413, 1938
- ¹³ McLanahan, S, and Stone, H B. Enterogenous Cysts. *Surg, Gynec and Obstet*, 58, 1027, 1934
- ¹⁴ Higgins, T T, and Lloyd, E I. Mesenteric Cysts. With a Report of Two Cases. *Brit Jour Surg*, 12, 95, 1924-1925
- ¹⁵ Miller, R T, Jr. Enterogenous Mesenteric Cysts. *Johns Hopkins Hosp Bull*, 272, 316, 1913

CYST OF THE SEMILUNAR CARTILAGE*

DeFOREST P WILLARD, M D

AND

JESSE T NICHOLSON, M D

PHILADELPHIA, PA

ALTHOUGH cysts of the external semilunar cartilages of the knee joint are no longer classed as rareties, very few of the mesial semilunar cartilage have been reported. A review of the more accessible literature revealed over 200 cases in all, reported prior to 1939. Among these, there are only 30 cases in which the lesion was in the internal cartilage.

There has been considerable controversy in the literature as to the etiology, physiology and pathology of these cysts. The etiology was accredited to trauma by a majority of the authors. Taylor¹⁵ advanced some of the best evidence in favor of the traumatic theory as follows. There was a history of injury in 30 per cent of the cases. Seventy-two per cent of the cysts occurred in the middle third of the cartilage, which was relatively unprotected by the patellar ligament and the lateral ligament of the knee.

A minority favored congenital or developmental origin. Ollerenshaw¹² particularly stressed the fact that although the internal cartilage was more frequently injured it was very infrequently involved by a cyst. He published a photograph of a cartilage removed from a female, age 11, in which the cyst was along the inner margin of the cartilage in the anterior third. He further cited instances of traumatic injuries with cartilage tears, in which a diagnosis of a cyst was made only upon removal of the cartilage. He reported several cases in which the cyst alone was excised, this recurred in every case.

In summing up the causes for cyst formation, Bennett and Shaw¹ found seven theories suggested by various authors. (1) Traumatic hemorrhage followed by mucoid degeneration of the hematoma. (2) Mucoid degeneration of the cartilage following trauma. (3) Injury to the blood or lymph channels producing a local change in the cell metabolism. (4) Obliteration of the paramenisceal arterioles causing degenerative changes in the cartilage. (5) Enlargement of certain cartilage cells with secretion of mucoid material into the connective tissue between them. (6) Trauma causing synovial implants in the cartilage. (7) Inclusion of synovia in the cartilage occurring during development.

Pathologically, the cysts were generally reported as multilocular, containing a gray to yellow gelatinous fluid. The stroma about the cysts was connective tissue. Most authors deny the presence of a lining to the cyst wall. Some recognize a flattened layer of connective tissue cells. A few (Ollerenshaw,¹² Klemberg,⁷ Zadek and Jaffe,¹⁹ Satanowsky,¹⁴ and Christmann⁴) reported an

* Presented before the Philadelphia Academy of Surgery, May 1, 1939. Submitted for publication June 22, 1939.

endothelial lining Two authors (Venezian and Christmann¹⁶) described villus projections into the cyst cavity

The case that we wish to present seems to fall into the developmental etiologic group

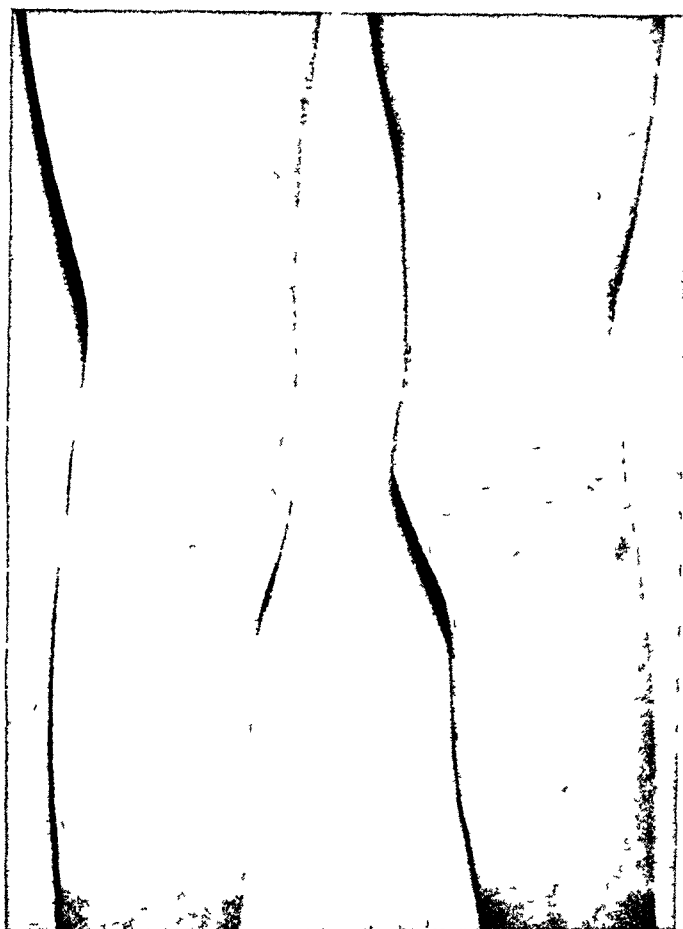


FIG 1—Objective appearance of a cyst of the left internal semilunar cartilage in a female, age 8

Case Report—C A, female, age 8, was examined December 2, 1938. A "lump" had been present on the inner side of the left knee for over a year. It had not noticeably increased in size. It gave no symptoms. There was no attributable cause. The medical history was irrelevant. On examination, a soft, fluctuant but firmly attached mass, approximately 9x1 cm, was palpable subcutaneously on the inner mesial side of the left knee (Fig 1). Knee motion was full, there was no tenderness or swelling.

Operation—January 12, 1939. A cystic mass was found, lying just anterior to the sartorius muscle and adjacent to the internal condyle of the femur. This was readily dissected free. As the joint space was approached, it was noticed that part of the internal lateral ligament was included in the wall of the cyst. With further dissection the joint space was opened and the cyst was found to be firmly attached to the internal cartilage. As dissection attempted to free the mass from the internal semilunar cartilage, a straw-colored, gelatinous, translucent fluid began to seep out. This indicated that the cartilage was involved. The tibial portion of the internal lateral ligament was found to include the distal portion of the cyst. This was dissected proximally to the joint cleft, and the cyst and internal semilunar cartilage were removed. The edges of the joint capsule were

plicated with silk sutures in an endeavor to substitute thickened capsule for the resected internal lateral ligament. The knee was immobilized with a plaster of paris bandage ap-

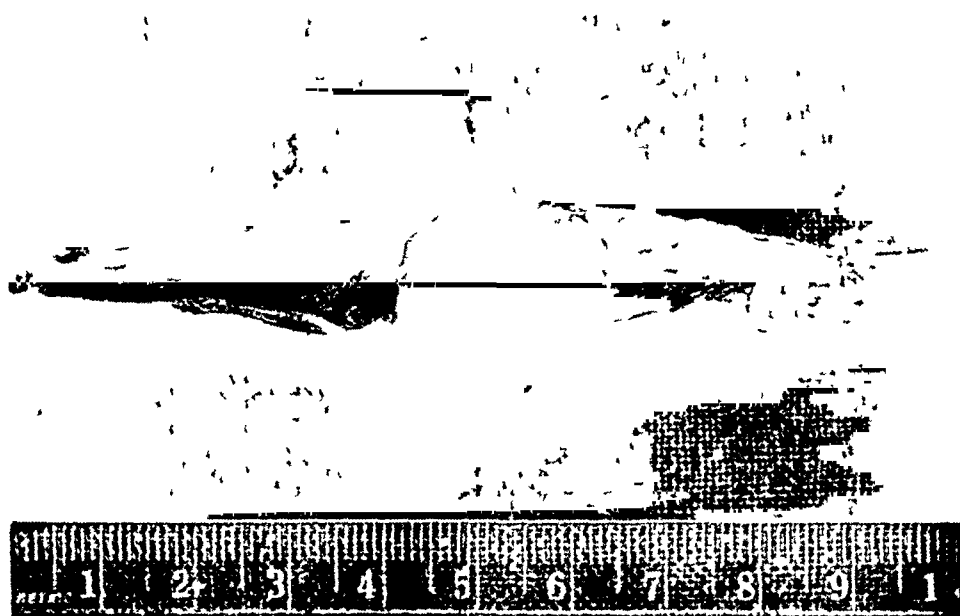


FIG 2—Photograph of the gross specimen (as viewed from the knee joint) showing the internal semilunar cartilage with the cystic expansion into the internal lateral ligament

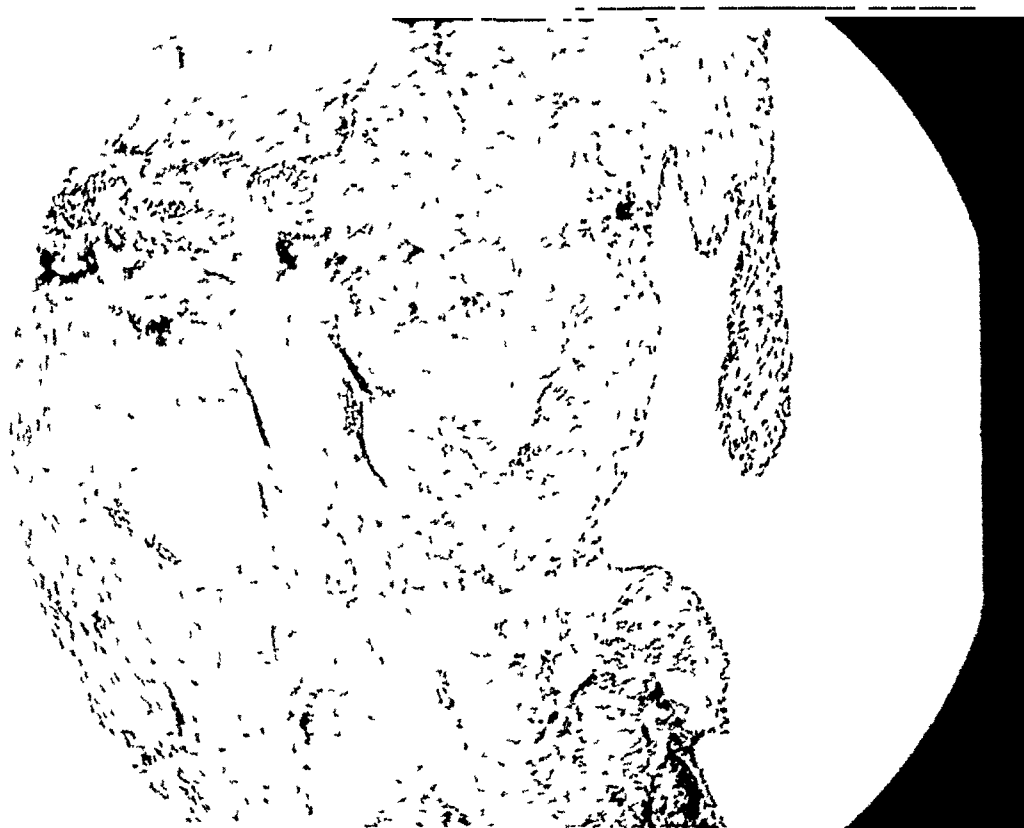


FIG 3—Photomicrograph showing a villus projection into the cyst cavity, an endothelial lining, the underlying connective tissue stroma, and the fibrocartilage of the meniscus

plied next to the skin from ankle to groin with the joint at 180°, and in as much varus as possible

Postoperative convalescence was uneventful. Muscle setting exercises for calf and

thigh groups were started the third day and weight-bearing the fifth. The plaster encasement was removed at the end of six weeks. There was no lateral mobility of the knee joint to indicate the loss of the internal lateral ligament. Active exercises against gravity were then instituted. In eight weeks there was full range of knee motion. Three months after operation the only difference in the two knees was the operative scar on the inner aspect of the joint and one-quarter of an inch atrophy of the thigh musculature on the left side.

Pathologic Examination—Dr. Arthur Waltz, of the Children's Hospital, demonstrated that the cyst was multilocular (Fig. 2). It involved the periphery of the middle third of the internal semilunar cartilage and internal lateral ligament of the left knee joint. The loculations had extended parallel to the ligament fibers. Microscopically, the cyst cavity was lined with a layer of flattened endothelial cells practically identical with those lining the smaller blood vessels (Fig. 3). Beneath the endothelial cells was a connective tissue stroma. There were several villus projections from this stroma into the cyst cavity. These villi were covered with the same endothelial cells. Beneath the connective tissue stroma was found the fibrocartilage of the meniscus.

Discussion—In the minds of the authors of this report, trauma does not account for the development of cysts of the semilunar cartilages. The age of this patient, age 8, and one reported by Colonna,⁵ age 6, both without history of injury, would indicate a minimal influence from a traumatic cause. The typical multilocular character of the cysts reported would be against a traumatic dissolution of cartilage cells resulting in the formation of a cyst cavity. The absence of pigment precludes hemorrhage into cartilage resulting from an injury. The microscopic findings of villi and an endothelial lining would strongly indicate a developmental fault as the etiologic factor.

SUMMARY

Cysts of the internal semilunar cartilage are relatively infrequent. There is considerable diversity of opinion as to the etiology of cysts of the semilunar cartilages.

The case under consideration is that of a female, age 8, in which the cyst involved the internal lateral ligament as well as the fibrocartilage.

The microscopic examination revealed definite endothelial lining and villus projections within the cyst cavity.

The evidence in favor of trauma as the (sole) etiologic factor is wanting.

BIBLIOGRAPHY

- ¹ Bennett, Geo. E., and Shaw, M. B. Cysts of Semilunar Cartilages. *Arch. Surg.*, 33, 92-107, July, 1936.
- ² Bogomolets, O. A. Genuine Cyst of Internal Meniscus of Knee. *Ortop i travmatol*, No. 1, 10, 98-100, 1936.
- ³ Campbell, W. C., and Mitchell, J. T. Semilunar Cartilage Cysts. *Amer. Jour. Surg.*, 6, 330, 1929.
- ⁴ Christmann, F. E. Cases. *Bolet y trab. de la Soc. de cir. de Buenos Aires*, 1936.
- ⁵ Colonna, Paul C. Cysts of the Internal Semilunar Cartilages. *Jour. Bone and Joint Surg.*, 15, 696, 1933.
- ⁶ Desplas, B., and Yovanovitch. Traumatic Cyst of External Meniscus. *Mem. Acad. de Chir.*, 62, 1023-1025, July 1, 1936.

- ⁷ Kleinberg, Samuel Cyst of the External Semilunar Cartilage Jour Bone and Joint Surg , 9, 323, April, 1927
- ⁸ Kirschner, F Ganglion of Meniscus of Knee Joint Question of Relation to Accident During Work Monatschr f Unfallh , 45, 22-26, January, 1938
- ⁹ Marchand, L, and Guibert, H L Cyst of Internal Meniscus of Knee, Analomicro-pathologic Study of Case Following Sprain Ann d'annat path , 15, 389-399 April, 1938
- ¹⁰ Meekison, D M Cysts of Semilunar Cartilages of Knee Joint Canad Med Asso Jour , Montreal, 36, 399-448, April, 1937
- ¹¹ Norinder, E Ganglion Acta ortop Scandinav , 7, 362-378, 1936
- ¹² Ollerenshaw, R Further Note on Development of Cysts in Connection with Semilunar Cartilages of Knee Joint Brit Jour Surg , Bristol, 23, 241-480, October, 1935
- ¹³ Ott, H W Ganglions of Meniscus and Injuries Monatschr f Unfallh , 43, 618-623, December, 1936
- ¹⁴ Satanowsky, S Cystic Degeneration of Internal Meniscus Semana med , 1, 881-886, March 19, 1936
- ¹⁵ Taylor, Herman Cysts of the Fibrocartilages of the Knee Joint Jour Bone and Joint Surg , 17, 588, July, 1935
- ¹⁶ Venezian and Christmann Referred to by Bennett and Shaw ¹
- ¹⁷ Wijnblad, H Wandering Ganglion of Meniscus Beitr z klin chir , 167, 177-188, 1938
- ¹⁸ Wolff, H Clinical Study Chir d org di Movimento, 23, 18-25, October, 1937
- ¹⁹ Zadek and Jaffe Referred to by Bennett and Shaw ¹

LOCKING ATTACHMENT FOR THE BALFOUR RETRACTOR

HAROLD D CAYLOR, M D

AND

MILES S HOUSER

BLUFFTON, IND

MOST SURGEONS using a Balfour retractor, particularly if the instrument has been in use for some time, have experienced the inconvenience of having the movable blade continually slip and relax the tension on the sides of the wound. A common practice is to tie a piece of gauze over the end of the instrument and around the movable blade to hold it in position.

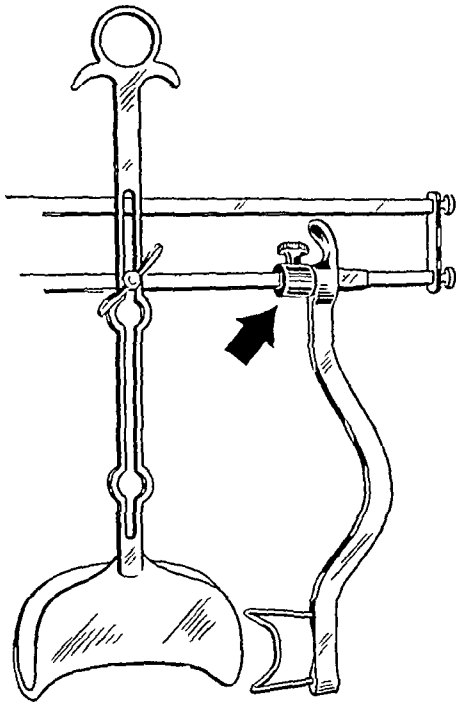


FIG 1 — Attachment on retractor indicated by arrow

This difficulty has been overcome by employing a simple device. The apparatus consists of a chrome-plated brass collar and set screw. The collar is approximately three-fourths of an inch in diameter and one-half inch long, with a square hole large enough to be a free fit on the sleeve (Fig 1). The set screw with knurled or wing-head is so designed that it will not back out and get free from the collar. This screw also locks the collar on the sleeve. A small hole the size of the screw should be drilled through the sleeve so the screw comes in contact with the bar. Since the movable blade of the retractor was designed to hold by friction, only a gentle pressure of the set screw is necessary to maintain the blade in position.

We have used this device repeatedly and have found it very satisfactory.

Submitted for publication August 18, 1939

BOOK REVIEWS

THE TREATMENT OF WAR WOUNDS AND FRACTURES By J TRUETA, M D New York Paul B Hoeber, Inc, 1940

THIS AMPLIFICATION of a small manual, which was published during the war in Spain, first in Catalanian, and later in Spanish, the author says, is the result of a demand not only from surgeons, but also the general practitioners who have been called upon during the military emergency to face the necessity of acquiring knowledge which they formerly had been content to regard as belonging to the surgeon. Though this expanded version is published after the close of the Spanish War, and "at a time when the world is at peace" (??), he is convinced that open fractures of civil life, road accidents, and those of industry do not differ essentially from those produced by aerial bombs, falling masonry, *etc*, and that the fundamental treatments are essentially the same, whatever may be the cause. He reveals in this book the necessity for keeping the word "war" in the title, for the subjects dealt with include the collection, transport, and evacuation of casualties, together with the treatment of neglected cases. Particular attention is given in this volume to a new problem of the present type of warfare, namely, the mass attacks directed against densely populated cities.

A report based upon his personal experience with a total of 1,073 cases of open fractures of the limbs, with but six deaths, demands that surgeons "stop, look and listen" at this time of impending world war. The almost uniform and simple methods of treatment of compound fractures, consisting of immediate débridement after reduction of the fracture, and immobilization in a plaster encasement, have certainly proven, in his experience, of special value in war-time.

The war in Spain provided the opportunity for a successful, large-scale study of the method, but the results of the study are certainly available for the benefit of victims of transport and industrial accidents in time of peace. Some 20,000 cases were treated by the same method, but detailed statistics of the results are not available at the present time. Trueta believes that the experiment was on a sufficiently large scale to justify the belief that the methods of treatment employed were responsible for his unbelievably low mortality. To add to this, among the bad results obtained, some 91, only four required amputation. To those who were engaged with the surgical care of the injured in the first World War these figures seem almost impossible.

The experience reported covers over 30 months of continual treatment of war casualties, including the immediate surgical treatment of casualties in 300 air raids. By rapid, properly planned, and boldly executed surgery, first advocated by Winnett Orr, followed by closed plaster of paris encase-

ment, the casualties can be spared the torment of having to spend the rest of their days crippled and mutilated

Triqueta feels that, in his experience, all the failures of the closed method of treatment of wounds are due to a failure to appreciate the general principles. Closed treatment should be employed only by those qualified by training to plan and undertake the first stages of the technic of debridement—which are purely surgical. It is completely fallacious, he warns, to believe that it suffices to close a wounded limb in a plaster of paris encasement to achieve the benefits of the closed treatment.

The book, which is pocket size, promises to become a testament not only to those who may in the future be called upon for duty in the medical corps of the armies, but also for those who may be engaged in traumatic surgery in civil practice.

It contains chapters on the historic survey of the development of military surgery, starting with Ambroise Pare and including the war of 1914-1918. It pays due credit to Orr, who, as a result of his experience in the World War, evolved the principles of treatment, which consist in (1) The importance of rest for the healing of wounds of soft tissues and bones, (2) the prevention of access of infected organisms to the tissues, and (3) immobilization, so that pain is reduced to a minimum and healing is allowed to proceed. No one at the present time can take issue with his first principle of débridement, nor with the second one of the removal of dead and infected tissue, and the prevention of the introduction of further infection. However, the use of the plaster encasement for immobilization has not been generally accepted, and he offers a summary of his reasons for believing that this is an essential factor in the Orr treatment.

(1) Rest allows local venous and capillary thrombi to form. These prevent and delay the spread of infection and are not broken down by repeated handling.

(2) Rest allows new capillaries to form which are not torn by repeated dressings of the wound.

(3) The plaster maintains a constant beneficial pressure on the wound, the calcium in it may be of local value.

(4) The mixture of organisms on the wound may by their mutual antagonism prevent the victory of any one group.

(5) To leave the wound uncovered, as advocated by Schede and Bohler, is good treatment for superficial wounds, but in the deep wounds produced by shells and aerial bombs, the dehydration and loss of heat which results from this treatment induces a condition of shock inimical to the general well-being of the patient and to the healing of his wounds.

This is truly a remarkable contribution, not only to military surgery but to traumatic surgery. When the authenticity of this report is vouched for by such men as Matas and Eloesser it can be accepted at par value.

WALTER ESTELL LEE

"HARVEY CUSHING'S SEVENTIETH BIRTHDAY PARTY" Published for the Harvey Cushing Society by Charles C Thomas, Springfield, Illinois, 1940

THE PRESENTATION in book form of the occasion of "Cushing's Birthday Party" has been made possible by the combined efforts of the Harvey Cushing Society and Charles C Thomas, Publishers, and provides an opportunity for his innumerable friends, students and admirers, outside the circle of the Cushing Society, to share the many tributes offered to this outstanding figure of American Surgery during the twentieth century

As stated in the preface, it is "Hail and Farewell," for while this tribute was in press Doctor Cushing died

"All things we ordain festival
Turn from then office to black funeral "

Truly the present and future generations should feel indebted to the Cushing Society for preserving the warmth, gaiety and intimacy of that occasion, for it was a remarkable event

The quotation from a letter received from the President of the United States is typical of this intimate friendship that was the spirit of the party

"The spirit of eternal youth is his It is not only his good fortune but the good fortune of all those who are privileged to call him a friend I think, too, it accounts for the fact that there has been no slowing down in his zest for life and for his work—a work which makes the human race his debtor and which has won him the plaudits of the great and the eternal gratitude of all sorts and conditions of men "

The volume includes not only the speeches given at the dinner, April 8, 1939, but also selections from letters and telegrams received by Doctor Cushing, together with a number of appreciations from the lay and medical press Further, there is an account by Dr Henry Viets of Doctor Cushing's case records written while he was an intern at the Massachusetts General Hospital, which deserves more than passing mention, for in these case histories there is definite evidence, at the beginning of his career, of the characteristics of a great man and a genius

To the six independent publications which have been previously issued in connection with "Cushing's Birthday," and as a supplement to his bibliography, this volume is a worthy companion, and should be in the library of every American physician and surgeon The intimacy of the tributes paid by his students and associates should and will serve as an inspiration to future generations, and no doubt will provide the nucleus for some Boswell to write a "Life of Harvey Cushing" comparable to the one which he wrote of Sir William Osler

WALTER ESTELL LEE

SHOCK BLOOD STUDIES AS A GUIDE TO THERAPY By John Scudder,
M D Philadelphia, J B Lippincott Co 1940

THE AUTHOR'S premise for the subtitle, "Blood Studies as a Guide to Therapy," may be stated very briefly. Two events, occurring separately or together, explain the circulatory failure in shock, loss of blood *in toto*, and the large obstacle to blood flow caused by a loss of blood plasma. Blood may be lost by hemorrhage or, according to accredited theory, by being trapped in its capillary bed by vasoconstriction. Loss of blood plasma may be caused by processes of dehydration, or by vasoconstriction, or, in the case of burns, by loss of proteins from the vascular compartment. A correct choice of reparative measures obviously requires appraisement of these various components of circulatory collapse. To this end, examination of the peripheral blood is clearly indicated. The author quite convincingly demonstrates the serviceableness of specific gravity measurements by the simple and rapid falling-drop method of Barbour and Hamilton. A measurement of whole blood specific gravity is often adequately informative. A more dependable definition of the underlying circumstances is, however, obtained by an hematocrit measurement using heparinized blood, and then determining the specific gravity of the plasma from the sample. Except as modified by hemorrhage, these measurements usually demonstrate hemoconcentration, or, in words more significant as regards circulatory failure, reduction of blood plasma volume. The utility of these simple measurements as a means of indicating therapeutic agents and observing their effectiveness is thoroughly illustrated by a large series of case records. Although their helpfulness is clearly demonstrated, the reader will not be surprised to find that the analysis and treatment of shock is not yet a rule of thumb procedure and for this reason remains an entertaining problem, for the contemplation of which these detailed records supply an excellent framework and the incentive of appraisement of the author's use of the evidence. The reader will profit greatly by studying them carefully. Here, in addition to replacement therapy, he will find applied the newest agent of plasma volume control, extract of the cortex of the adrenal gland, a probably reasonable experiment in therapy even though direct evidence of failure of function of the adrenal cortex in shock is lacking. The author, being aware that examination of the peripheral blood will not define the *extent* of blood and extracellular fluid losses, has emphasized the well established requirement for estimation of the position of body fluid balance in situations which have produced shock.

The book is much more extensively informative than the subtitle suggests. It is also an excellent "guide" to the historic and experimental development of current conceptions of shock, with a proper emphasis on the relationship of body fluid disturbances to circulatory failure. In this direction a resumé of the functions of the adrenal cortex is included.

A large item in the book is the author's advocacy of plasma potassium increase for a prominent position in the pathogenesis of shock. The premise

used is a vasoconstrictive action of potassium and a deleterious effect on the heart. The author presents a large amount of evidence in support of his accusation of potassium. All of it is, however, entirely circumstantial. Direct proof that the levels of plasma potassium found in patients in shock cause either vasoconstriction or cardiac embarrassment is not provided. Study of the data presented does not at all convincingly describe a relationship of potassium concentration to degree of shock. Increase in plasma potassium is easily understandable as a result of disturbance of extra- and intracellular fluid adjustments. That it has an especial significance among many concurrent distortions of the plasma structure and changes in the physical properties of the blood is obviously difficult of proof. By the same token, the author's indictment of potassium cannot be dogmatically denied. At any rate since, as the author admits, vasoconstriction as evidenced by hemoconcentration precedes the accumulation of potassium in the plasma, potassium is clearly not the long sought agent of that basal happening. But denying potassium a primary rôle does not remove the important question which the author has raised of its position among the many circumstances which determine the eventual outcome in shock. The above comments are intended only to indicate the intricacies of this problem and the unwillingness of this reviewer to be convinced by the evidence at hand.

JAMES L. GAMBLE

DIVERTICULA AND DIVERTICULITIS OF THE INTESTINE. Their Pathology, Diagnosis and Treatment. By HAROLD C. EDWARDS, M.S. (Lond.), F.R.C.S. (Eng.). Surgeon and Lecturer in Surgery to King's College Hospital, London. With Foreword by Gordon Gordon-Taylor, O.B.E., M.S., F.R.C.S. With 223 illustrations, many in color. William Wood Medical Books, Baltimore, 1939.

This work is in substance the Jacksonian Prize Essay of the Royal College of Surgeons for the year 1932, revised and brought up to date. It represents the result of a personal investigation of clinical cases the data of which were obtained from the case histories of patients suffering from symptoms due to the presence of diverticula, or in whom diverticula were found at operation, postmortem, or revealed during a roentgenologic examination. The majority of these cases were examined personally. In addition, a questionnaire was circulated to all patients in whom diverticula were found roentgenologically.

The pathologic specimens are from various sources. Some are recent operative specimens from the author's own cases or those of colleagues. For most of the cases in the unusually rich series of colovesical fistulae, the author is greatly indebted to the late Sir John Thomson-Walker, who furnished him with the notes of many of his private cases. Others have been obtained at postmortem examinations performed during the past 16 years. A number are from museum shelves. All these have been taken out of their bottles for re-

investigation. The author is indebted to the curators of museums other than that of his own school for the loan of some of the specimens examined and described in the text.

The roentgenographic material is derived chiefly from King's College Hospital during the period 1925-1937, inclusive. A few only of the prints were obtained from colleagues and other sources.

There are numerous excellent articles available in the American surgical literature dealing with the frequency of diverticula, their probable etiology and their treatment. A student, however, has some difficulty finding a monograph dealing with the subject in a comprehensive manner. Doctor Edwards' book is, therefore, timely, but would have been of still greater value if it had included diverticula of the entire alimentary canal.

In the introduction the author deals with the classification of diverticula. He divides them into congenital and acquired. The first group is composed almost exclusively of Meckel's diverticula to which he adds a few other rare congenital diverticula not of Meckelian origin. The second, or acquired, group is subdivided into those arising from the duodenum, jejunum and ileum, colon and vermiform appendix.

Section I deals with the congenital types. The subject is well presented especially in regard to the clinical significance of pathologic conditions which may affect Meckel's diverticulum.

Section II is devoted to diverticula of the duodenum. It calls attention to the increased frequency with which this condition is being reported, apparently due to improved radiologic technic and interest in the subject. The radiologic appearance of these lesions is well illustrated. One slide shows a microscopic section indicating the protrusion of the diverticulum between muscle fibers, and thereby presents evidence of being acquired rather than congenital in nature. This point is further emphasized in special chapters on morbid anatomy and pathogenesis, which present a critical discussion which is recommended to those interested in the subject. The author further calls attention to the frequent association of duodenal diverticula and diverticulosis of the colon, and believes that, because the morphology and age incidence are identical, the same factors are responsible for their development. A special chapter devoted to ulcer-diverticula of the duodenum is very interesting and well illustrated. In the chapter on operative technic, he justly calls attention to the dangers involved, and describes the technic advocated in diverticula affecting the different portions of the duodenum. The value of this chapter to the reader would have been increased by a discussion of indications for operation. This phase is but slightly touched upon in Chapter X under the heading "The Clinical Aspect."

Section III is well illustrated with a wealth of clinical and postmortem material pertaining to diverticula of the jejunum. The chapter on pathogenesis is excellent. Although the condition is held to be relatively uncommon and of little clinical importance, complications of perforation, acute diverticulitis,

acute obstruction and volvulus are described. Medical and surgical treatment is discussed.

Section IV deals with diverticula of the large intestine, including the appendix. It comprises about half the book—which is in accordance with the clinical importance of these lesions. The author presents interesting statistics on incidence which, in general, correspond to those observed in this country. He shows, on the basis of anatomic and microscopic material, that these diverticula emerge at the points of entry of blood vessels. There are beautifully colored illustrations showing the early stage of development. Considerable attention is paid in Chapter XXII to the radiologic aspect, and it is richly illustrated. Treatment of diverticulosis and uncomplicated diverticulitis is medical, which consists of the prevention of stasis in the diverticula. The methods employed are avoidance of constipation, reducing the bulk of undigested and indigestible food and colon lavage. Indications for operation are discussed in those uncomplicated cases with persistent symptoms, recurrent exacerbations, and persistence of bladder symptoms. The various operative procedures which may be utilized are presented.

Diverticulitis with complications is discussed in detail, together with the different operations which may be employed during the acute stage of perforation or for one of the later sequelae.

Among 162 cases of diverticula of the colon, nine were associated with a new growth (5.6 per cent).

The final chapter is devoted to diverticula of the vermiform appendix, and is followed by a very complete bibliography.

The review of this excellent book has been instructive and profitable and it is unhesitatingly recommended to physicians as well as surgeons.

CARL EGGERS

MEMOIR

GEORGE W W BREWSTER

1866-1939

GEORGE W W BREWSTER died suddenly at his home in Boston, September 26, 1939, in his seventy-fourth year. He was born in Roxbury, Massachusetts, March 26, 1866, and prepared for college at the Roxbury Latin School. He was graduated from Harvard College in the class of 1889, and received his M D degree from the Harvard Medical School in 1893. He served as surgical intern at the Massachusetts General Hospital following his graduation, and soon afterwards became private assistant to Dr. Maurice H. Richardson. He was one of the first of the group of distinguished assistants of a distinguished master, and ever afterwards gratefully acknowledged his indebtedness to that great teacher of sound surgical principles.

In 1900, he was appointed Surgeon to Out-Patients at the Massachusetts General Hospital, becoming Assistant Surgeon in 1906, and Visiting Surgeon in 1914. In 1927, at the completion of 27 years of active surgical service, he reached the retiring age at that hospital and was appointed to the Board of Consultation. He was also surgical consultant to the Chelsea Memorial Hospital, Chelsea, Mass., Leonard Morse Hospital, Natick, Mass., Milford Hospital, Milford, Mass., and Beth Israel Hospital, Boston, Mass.

He carried on an active surgical practice until within the last few years when increasing ill health incapacitated him for such taxing work. He bore the heavy burden of a distressing chronic ailment with great fortitude and cheerfulness.

He is survived by his widow, Ellen Hodge Brewster, and three sons: William L., George W. W., Jr., and Henry H., M.D.

George Brewster was a lineal descendant of Elder William Brewster who came over in the Mayflower and landed on the Rock at Plymouth. The mellowing influences of time, space, and freedom in the New World have happily softened, in their prolific progeny, some of the granitic qualities of the early Puritans, notably their austerity and intolerance, but the sterling underlying qualities of character and purpose of the Fathers are clearly discernible in the salient traits of this son of that hardy stock.

George Brewster loved with the utmost loyalty his family, his profession and his friends—all that made his life.

He was a clinical surgeon of great ability and skill. His diagnostic acumen acquired before the days of roentgenology and elaborate laboratory tests seemed intuitive and almost uncanny. His judgment was sound, and he knew both how and when to operate and when to withhold his hand. In acute abdominal emergencies he was perhaps at his best. Quick, deft, and unhesitating,

he went direct to the lesion with the least possible damage to surrounding tissues. He excelled also in the delicate surgery of the neck and thyroid gland. His interest in the patient did not cease with the operation—he took infinite pains with the after-care, and knew how to make a sick man comfortable and happy. The most forlorn ward patient would smile at his approach.



GEORGE W. W. BREWSTER, M.D.

He was free from every affectation except one harmless one, he delighted in pretending to be completely at a loss as to how to proceed in the midst of an operation in order to draw out some ingenuous advice from an unwary assistant. He hated sham and pomposity and was an adept at exposing the one, and deflating the other with outspoken candor. His frankness at times was

almost appalling but no one could take legitimate offense when the intent was always kindly

He was immensely popular with his fellow-man, and belonged to many professional societies and social clubs. He was elected to the American Surgical Association in 1917. There never was a more loyal member, or one who enjoyed the meetings more than he, and none received a warmer welcome from their many friends than Dr and Mrs George Brewster. He was not a frequent contributor of papers but he followed the presentations of others with keen interest and extraordinary patience, his comments, not from the platform, but in a low tone to his intimates on the seats, were succinct, to the point, and usually appreciative.

He never occupied a professorial chair, but as an unacademic teacher of good, sound surgery he deeply influenced a very considerable group of students, interns, assistants and consultants who cherish the memory of his dynamic sayings and brilliant demonstrations. Brought up as he was in the older school of what is now regarded as rough and ready surgery, he always kept an open mind, and was keenly interested in, and receptive to, the newer advances.

He liked young men and followed their careers with genuine interest. He loved the old M G H, and up to the very end, was almost a daily visitor at clinics and staff conferences, where his genial presence and sound criticism and advice were always welcome. He was greatly beloved by young and old, he never grew old himself, he was unique, he did great good in the world, and is sorely missed by a host of friends. May his genes endure.

LINCOLN DAVIS

EDITORIAL ADDRESS

Original typed manuscripts and illustrations submitted to this Journal should be forwarded prepaid, at the author's risk, to the Chairman of the Editorial Board of the ANNALS OF SURGERY

Walter Estell Lee, M D
1833 Pine Street, Philadelphia, Pa

Contributions in a foreign language when accepted will be translated and published in English

Exchanges and Books for Review should be sent to James T Pilcher, M D, Managing Editor, 121 Gates Avenue Brooklyn, N Y

Subscriptions, advertising and all business communications should be addressed

ANNALS OF SURGERY
227 South Sixth Street, Philadelphia, Pa

ANNALS OF SURGERY

VOL 112

SEPTEMBER, 1940

No 3



CONGENITAL ANOMALIES OF THE DUODENUM

JOHN B DE C M SAUNDERS, M B , C H B , F R C S (Ed),

AND

HAROLD H LINDNER, M D.

SAN FRANCISCO, CALIF

FROM THE DEPARTMENT OF APPLIED ANATOMY AND DIVISION OF SURGERY, UNIVERSITY OF CALIFORNIA MEDICAL SCHOOL,
SAN FRANCISCO, CALIF

CONGENITAL ANOMALIES of the duodenum are of sufficient rarity and interest to warrant a report when encountered We have had the fortune to



FIG 1—Case 1 Radiograph three hours after barium meal showing almost complete retention A minute quantity of barium has passed into the proximal jejunum

examine and study, in some detail, three cases These cases have offered the opportunity of assessing the various theories as to their etiology and of

Submitted for publication June 29, 1939

examining, in this respect, several details of duodenal development which serve to clarify the subject. In addition, a short review of the classification, incidence, diagnosis and treatment of such anomalies is considered.

The following is a short resumé of the three cases which prompted our interest in this subject. The first of them illustrates an example of congenital

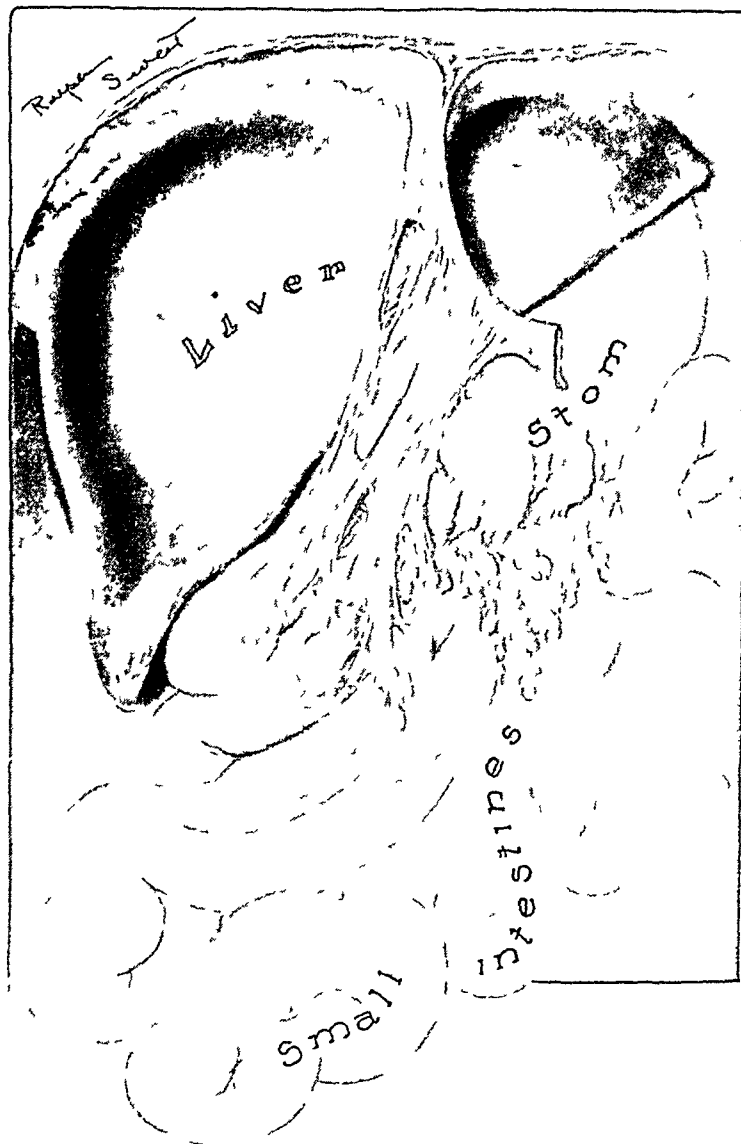


FIG. 2.—Appearances on opening abdomen in Case 1. The hepato duodenal adhesions fix the coiled duodenum against the greater curvature of the stomach. The colon is not visible as owing to nonrotation it lies behind and to the left of the small bowel.

duodenal stenosis associated with nonrotation of the intestine, the second, of congenital duodenal valve formation, and the third, a case exhibiting abnormalities of shape, position and fixation. All these cases were associated, as is so common in congenital malformation, with other anomalies.

Case 1—Baby H, male, birth weight 7 lbs 10 oz. The baby was spontaneously delivered at term, markedly jaundiced. Meconium was passed at the end of the first 24

hours On routine formula, the infant nursed poorly On the third day, the child regurgitated large quantities of sour-smelling food but passed a large brownish-yellow stool From the third to the seventh day, he vomited repeatedly The intensity of the jaundice increased and the child rapidly lost ground There was a weight loss of 18 oz by the seventh day

Physical Examination—March 26, 1938 There was considerable loss of tissue turgor and deep icterus The abdomen was distended in both upper quadrants and reversed gastric peristalsis was observed after feeding No pyloric tumor was palpable but considerable gastric dilatation was determined There was bilateral talipes equinovarus Radiographic examination revealed dilatation of both esophagus and stomach with con-

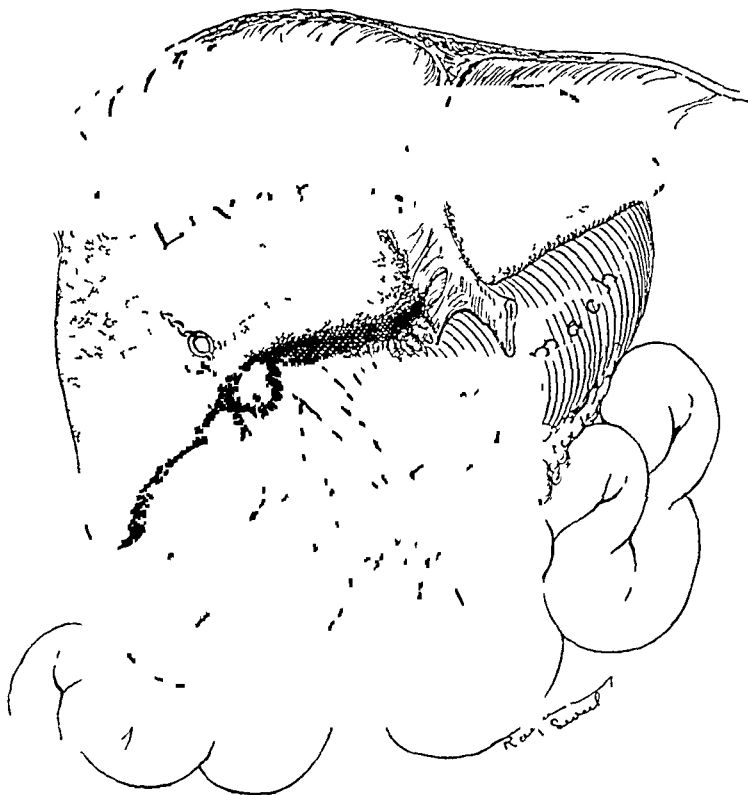


FIG 3—Case 1 Following division of peritoneal adhesions

siderable food retention No barium passed the pylorus At three hours, retention was almost complete (Fig 1) However, a minute quantity of barium was seen in the proximal jejunum *Preoperative Diagnosis* Pyloric stenosis or spasm

Operation—March 26, 1938 Following preoperative supportive measures celiotomy was carried out The liver presented early and although of normal size, its unusually mottled brownish color was noted The transverse colon was absent from its usual position below the greater curvature of the stomach, being replaced by coils of small intestine The colon was found accumulated on the left side, indicating nonrotation The pyloric region was obscured by a persistent hepatoduodenal ligament (Fig 2) On division of this peritoneal ligament, the duodenum was found matted together by adhesions in the form of an S-shaped loop and fused with the greater curvature of the stomach below the pylorus (Fig 3) On further dissection the curvature of the duodenum was restored, it being found to be unfixed, suspended by a mesoduodenum

A stenotic area, three-quarters of an inch long, reducing the bowel caliber to one-eighth of an inch, involved the proximal segment of the second and distal portion of the first part of the duodenum (Fig 4) On longitudinal incision of this area, a lumen the size of a pencil lead was encountered The openings of the pancreatic and biliary ducts were not observed The diameter of the lumen was increased by closure of the incision

transversely, as in the Heinecke-Mikulicz procedure, and the lumen now judged to be of adequate size. After closure the child was returned to bed in fairly good condition.

The postoperative course was uneventful, except that the infant vomited once on the second day. He was discharged on the seventh postoperative day.

Subsequent Course—Fifteen days after operation the child died, following a convulsion associated with a respiratory infection. Autopsy was refused. Jaundice, though decreasing, persisted up to the time of death.

Case 2—S. M. W., age 7½, white, was brought to the University of California Hospital, because of frequent and persistent vomiting since one month following birth. The

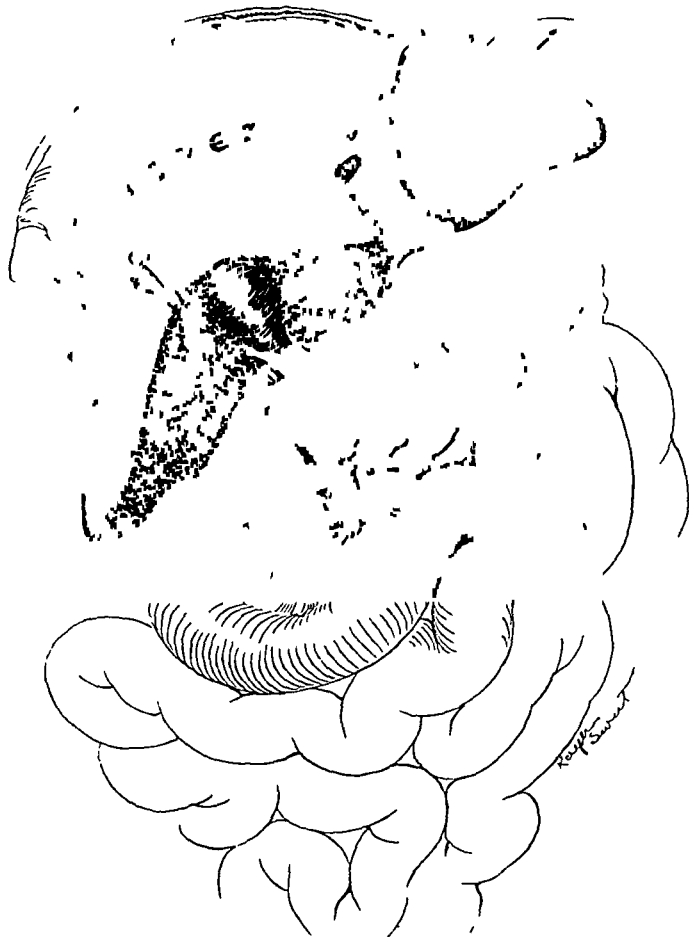


FIG. 4.—Case 1. The duodenal loop has been freed by further dissection of adhesions. The stenotic area and the unfixed mesoduodenum are clearly shown.

child had been apparently normal up to the age of one month, at which time she began to have spells of projectile vomiting following each feeding. During the next two months the child dropped from a birth weight of 7¾ lbs. to about 4 lbs. At the age of three months, the child was taken to a private hospital where she remained for the next nine months. The vomiting continued and her weight increased to 9 lbs. At 15 months, vomiting persisting, a preoperative diagnosis of congenital hypertrophic pyloric stenosis was made and celiotomy performed. Examination revealed a large gaping pylorus, many veil-like adhesions from the gallbladder to the duodenum, a large mesoduodenum and a uniform collapse of the distal two-thirds of the duodenum and small intestine. Many enlarged lymph nodes, thought to be tuberculous, were found in the mesentery. A long Meckel's diverticulum was present. There was no operative intervention and a postoperative diagnosis of "tuberculosis of the mesentery and intestines" was made.

Subsequent Course—The child remained a hospital case until the age of three, continuing to vomit, and on discharge her weight was only 18 lbs. For the following four years, up to the age of seven, and her entry into the University of California Hospital, the child continued to vomit after each meal, at times bringing up food eaten several days previously. She gained weight slowly, and was constantly under medical care for seven years. Physical examination on entry showed an underweight, pallid, dehydrated child. No visible peristalsis or palpable organs. No other positive findings. Laboratory data were essentially normal, including a negative tuberculin test. Radiographic examination, made on entry, seemed to indicate a definite obstruction in the second or third portion of

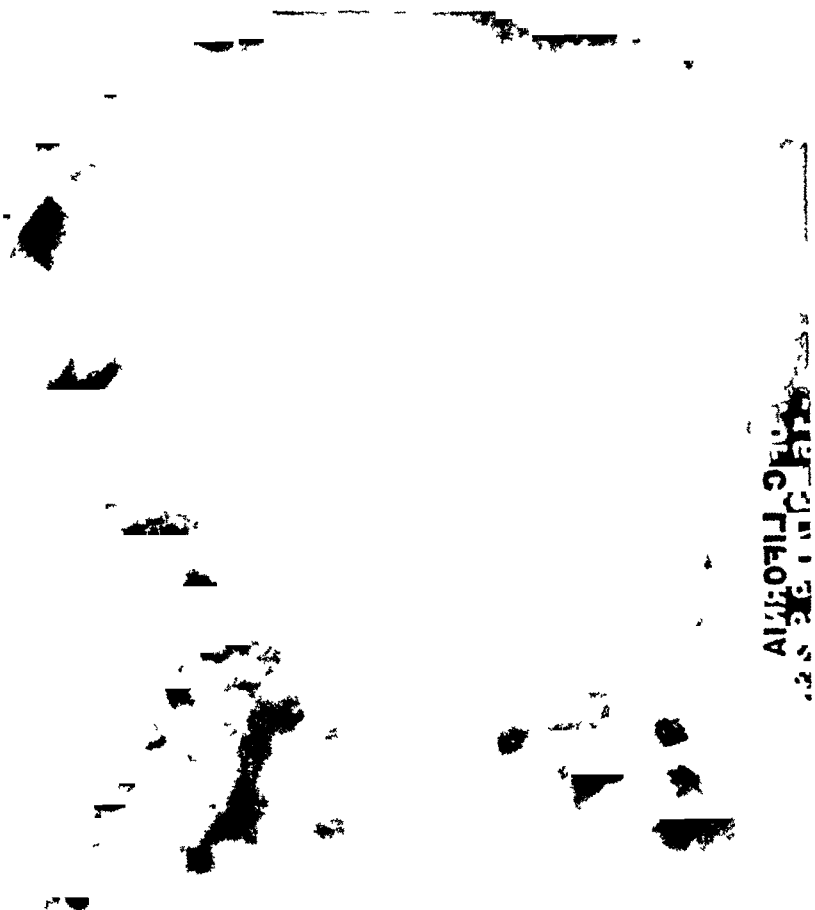


FIG 5—Case 2. Radiograph three hours after barium meal showing dilated stomach and megaduodenum with obstruction.

duodenum (Fig 5) *Preoperative Diagnosis* Congenital stenosis of the second or third part of the duodenum.

Operation—April 19, 1937. The transverse colon and omentum appeared to be normal. The mesentery of the small bowel and duodenum contained many hard, enlarged lymph nodes of varying size. The entire small bowel distal to the ligament of Treitz was moderately collapsed and appeared quite normal. The stomach was markedly dilated and flabby and extended well down into the pelvis. The stomach walls were very thick. The pylorus admitted three fingers, and the first and a part of the second portion of the duodenum were markedly dilated and hypertrophied. The common bile duct was moderately dilated and entered the duodenum at an abnormally high position. The cecum had not descended from under the liver and was suspended by a mesentery.

In view of the foregoing findings it was decided that the procedure of choice was mobilization of the duodenum to determine the cause and site of the obstruction rather than a palliative gastro-enterostomy. Upon freeing and rolling up the duodenum, a

circular ring of constriction, four inches distal to the pylorus, was found. The third and fourth portions of the duodenum distal to this constriction were of normal size. An incision was made directly over the constricted area and a diaphragm was encountered, completely occluding the lumen save for a small perforation anteriorly, which barely admitted the tip of the little finger. The diaphragm was completely excised and the bowel was closed in the Heinecke-Mikulicz manner to prevent stenosis. The child did extremely well postoperatively, taking food by mouth without vomiting and rapidly gained in weight. When last seen, March 29, 1939, two years later, she had no gastro-intestinal symptoms and was now up to normal weight for her age.



FIG. 6—Appearances in Case 3 viewed from below and the right. The cecum is fixed to the under surface of the liver and below it the highly constricted and obstructed duodenum may be seen.

Case 3—A C, female, age 3 weeks, was brought to the University of California Hospital, August 6, 1934, because of a large, protruding umbilical mass and persistent projectile vomiting for the two weeks previous to entry. The child was born at term and delivered normally. The umbilical mass was observed at birth. It slowly increased in size and became gangrenous. Foods were poorly taken, the child exhibiting projectile vomiting at the end of the first week, which continued until the time of hospital entry. At entry, the child was markedly emaciated and dehydrated. The umbilical mass was large, dark brown, cylindric in shape, protruding some three inches beyond the abdominal wall. It was covered by a thick, hard seal, from beneath which a foul-smelling, brownish, serous fluid exuded. The mass was kept under considerable tension by intra-abdominal pressure. There was a ring of unhealthy granulation tissue at the junction of the mass with the abdominal wall. Methylene blue given orally did not appear in the mass or its

discharge After routine preoperative care, the protruding gangrenous tissue was removed, the area left gradually granulating in, and the child was discharged, September 16, 1934 Pathologic examination of the material showed the presence of liver tissue

Subsequent Course—During the next three months, while at home, the child did poorly, vomiting at frequent intervals On December 15, 1934 she was returned to hospital The umbilical wound was well healed although marked divarication of the rectus abdominus muscle was noted Vomiting continued and on January 9 1934 the child contracted a bronchopneumonia from which she expired, January 11, 1935

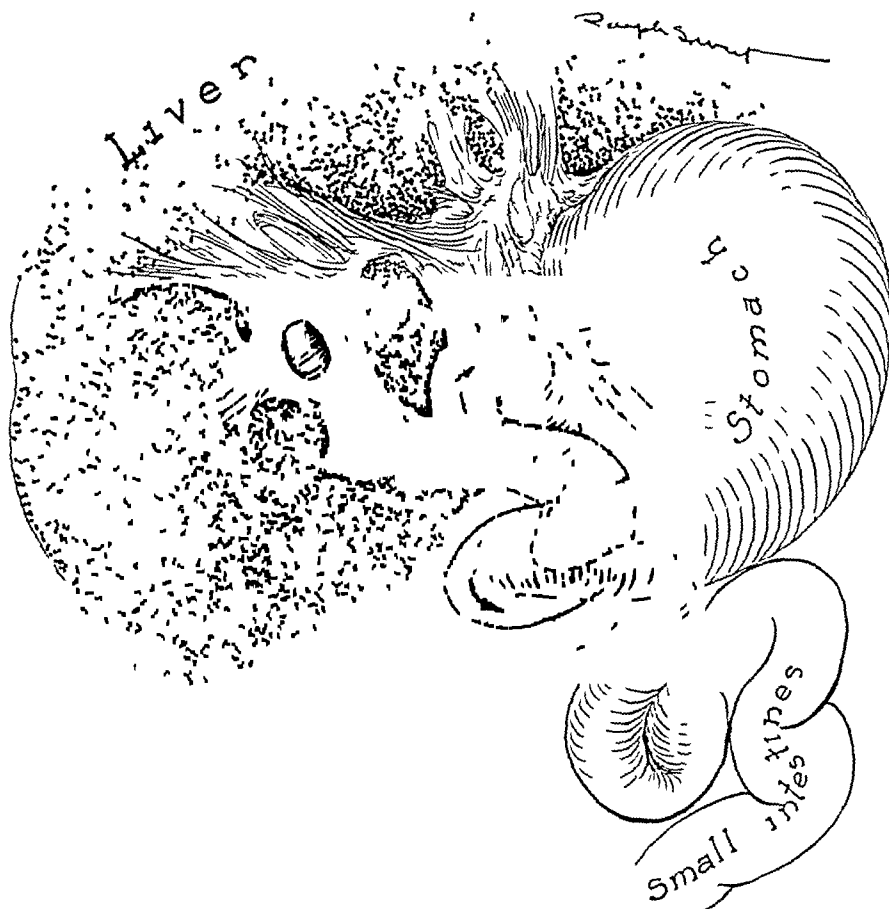


FIG 7—Case 3 Semidiagrammatic illustration showing the position and evolution of the abnormal duodenum

Autopsy (Fig 6)—The liver was extremely large and hard, and extended down to the upper limits of the right iliac fossa There was a scarred area on the anterior surface of the liver in the region of the umbilicus, obviously the area of herniation There was an anomalous right lobe of the liver A single umbilical artery extended from the hypogastric vessels to the liver where it entered an abnormal porta hepatis The artery was elevated from the posterior surface of the anterior abdominal wall being enclosed in a mesentery It formed, with the posterior abdominal wall, a boundary which divided the peritoneal cavity into two parts, a small right and a large left portion The alimentary tract exhibited incomplete fixation The stomach was of normal size and occupied its approximate normal position There was a marked duodenal anomaly present The first portion extended horizontally to the right and was then abruptly reflected upon itself, in the form of a U, to the region behind the pyloric antrum It then ascended obliquely upward and to the right, making an abrupt flexure behind the liver to extend in a sharp curve, downwards and to the right, making still another flexure behind the first portion of the duodenum, and passed horizontally to the left where it terminated in the duodenojejunal flexure (Fig 7) It was interesting to note that in this case the

duodenum was so markedly convoluted as to mechanically offer obstruction despite the complete lack of actual peritoneal fixation

Congenital obstruction of the duodenum received much attention in the latter half of the last and at the beginning of the present century. This was to be expected as the outcome of the reconstructive methods introduced into embryology by His, in 1868. Comprehensive articles were published on the continent by Thoremin⁴¹ (1877), Kuliga²⁹ (1903) and Kreuter^{27 28} (1905, 1909), in America by Cordes⁸ (1901), and in England by Clogg⁷ (1904) and Spriggs³⁸ (1912). The foremost recent discussions are those of Davis and Poynter⁹ (1922) and of Ladd³⁰ (1933).

It is difficult to determine with any accuracy the number of cases reported as the literature is in some confusion. Spriggs,³⁸ however, stated, in 1912, that congenital duodenal obstruction "is not so very much rarer than imperforate anus as one might expect, the one affection being so obvious cannot be missed, the other most certainly is not so constantly in the mind of the practitioner and not so obvious, hence it often is missed." That the duodenum is a common level of congenital obstruction is indicated by Davis and Poynter.⁹ These authors studied 392 cases of congenital intestinal obstruction, of which 134 occurred in the duodenum.

Attempts have been made to estimate the incidence of congenital obstruction in the general population at infancy. Again the figures are too unreliable to be of much service except to indicate the comparative rarity. Such figures are given by Ernst¹¹ (1916), two cases of intestinal atresia in 41,000 children in the Royal Lyng-In Hospital, Copenhagen, and Thoremin,⁴¹ nine cases in 150,000 at Petrograd, and two in 111,451 born over an 11-year period at Vienna.

Pathology—Pathologically congenital duodenal obstruction has been found to result from the effects of either intrinsic or extrinsic factors.

Extrinsic obstruction of the duodenal lumen has been described as the result of either developmental error or prenatal pathologic processes. Among developmental errors may be listed kinking of the bowel from lack of fixation or abnormal fixation, massive volvulus, persistence of a hepatoduodenocolic ligament, annular pancreas and vascular anomalies with aberrant vessels. Among prenatal pathologic processes which have been encountered may be mentioned abnormal adhesive bands, mesenteric cysts and neoplasms of related organs such as the liver or pancreas.

Intrinsic obstruction is the outcome of atresia, amounting in some instances to complete suppression of a segment of the intestine, stenosis, or valve formation. It has been stated (Cordes⁸ and Clogg⁷) that complete atresia is more frequent than stenosis in all situations, and that both atresia and stenosis are much more frequent than valve formation. These forms are sometimes associated with abnormalities of the biliary tract. The bile duct may have an abnormal site of implantation, draining on occasion into the stomach or entering the duodenum at an unusually low level. In some instances doubling of the bile duct has been reported, each duct emptying at a different level. In-

intrinsic obstruction occurs either above, at, or below the ampulla of Vater. It is impossible to give any very satisfactory opinion of its frequency at any level. It would seem, however, that the great majority of obstructions occur in the second portion of the duodenum immediately above or immediately below the duodenal papilla. Davis and Poynter⁹ cited 59 cases above and 75 below, Cordes,⁸ 20 above and 13 below. The exact location is so frequently not reported that statistical conclusions are impossible. A small percentage of cases of duodenal atresia or stenosis are associated with stenosis or atresia of one or more segments of the alimentary tract.

In extrinsic obstruction the etiologic factor is so readily demonstrable, either at the operating or postmortem table, as to require no further comment.

For intrinsic obstructions, however, a wide variety of theories, many now of only historic interest, have been propounded. Such views include fetal intussusception, enteritis, localized spasm, Meckel's discarded segmentation theory, segmental atrophy, local vascular thrombosis or embolism, hypertrophy of the valvulae conniventes, *etc*.

A theory widely held is based on the dictum of Bland-Sutton³⁹ that abnormalities tend to occur at the sites of embryologic events. As the biliary and pancreatic systems arise from the second part of the duodenum, this view has been accepted as the determining factor for the presence of the obstruction at this level or in its immediate neighborhood. This theory has the attraction of simplicity and is without doubt, for some regions of the body, such as the branchial region, of the greatest significance. In this instance, however, we find the theory highly questionable if not wholly unacceptable, as the greater percentage of intrinsic obstructions of the duodenum occur relatively distant from the entrance of the biliary duct. In addition, exactly similar pathologic processes, occasionally concomitant, occur at other levels of the small intestine where development is unassociated with any special embryologic event in the Bland-Sutton sense. The pathologic processes being the same, it is reasonable to suppose that the factors responsible for atresia or stenosis in the duodenum and at other levels of the bowel are similar.

A hypothesis which requires more serious consideration because of its almost universal acceptance is the outcome of observations made by Tandler,⁴⁰ in 1900, on the formation of the duodenal lumen. This author pointed out that during development the duodenal lumen becomes completely obliterated (fifth to sixth week) by an extraordinary proliferation of its epithelial lining. This proliferation appears to completely block the lumen although this has been questioned by Frazer.¹³ It has been assumed (Kreuter²⁷) that persistence of this state is responsible for atresia, stenosis and membrane formation. However, similar objections arise as in Bland-Sutton's theory, for atresias occur at levels which are stranger to such a process of proliferation.

Wyss has propounded a view that the disturbance is the outcome of interference with vascularization and often associated with changes in the vascular pattern. He describes two cases with absent pancreaticoduodenal arteries. This view is not to be confused with extrinsic obstructions caused by

anomalous vessels. It is well recognized that changes in vascular pattern are common in congenital anomalies but this does not mean that the changes are the primary cause of the anomaly and have not arisen secondary to the deficiency in the area supplied by the vessel.

Embryology—It goes without saying that a necessary preliminary to an understanding of anomalies of position, and to a discussion of the possible mechanism of atresia or stenosis, is a review of the chief events in the developmental history of the duodenum. The outline of events herein described is based upon a series of dissections of the embryo at various stages, carried out

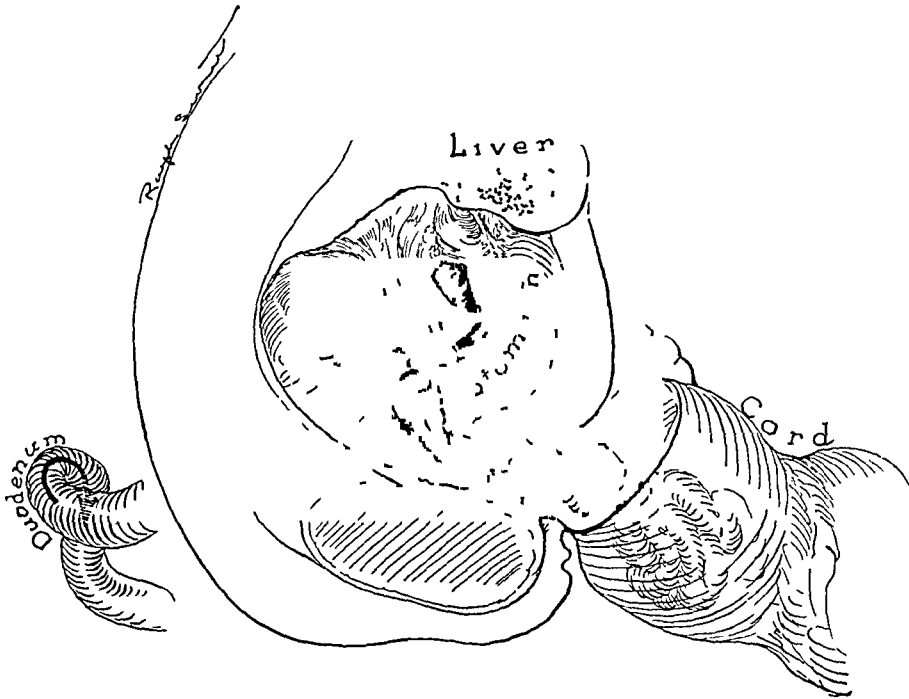


FIG. 8.—Dissection of an embryo of 13.5 Mm CR length viewed from the right anterior aspect. The liver has been excised exposing the opening of the omental bursa and the severed portal vein. Note the formation of the primary duodenal curves at this stage. The enterocolic segment occupies the umbilical cord. Inset shows the simplicity of the primary curves.

under the microscope. It is felt that such a method gives a far more accurate picture of morphologic details than the more usual technic of reconstruction.

We have found it convenient to divide the development of the duodenum into four stages.

Stage I—Rudimentary Stage. At this stage the duodenum is recognized as the segment of the primitive gut lying between the dilatation of the stomach and the commencement of the enterocolic loop. We regard the duodenal segment as constituting, at an early stage, a distinctive part of the alimentary tract. Supported by a thickened portion of the common dorsal mesentery, the biliary system has already made its appearance, and at 5 Mm the dorsal pancreatic rudiment has budded into the mesoduodenum.

Stage II—Formation of Primary Curves (Fig. 8). As development proceeds, the stomach undergoes rotation to assume its permanent position, and as it does so, the future omental bursa is defined. Meanwhile the enterocolic

loop has elongated and proceeded to occupy its position at the root of the umbilical cord. The duodenum has likewise participated in the changes. These involve predominantly its first portion. This part shows a far greater degree of elongation than the rest. At 13.5 Mm it is large and well developed and is almost twice the diameter of the succeeding portion of the intestine. It extends transversely across the abdomen with a very slight upward inclination and is highly arched over the vitelline or future portal vein. Passing dorsally, it

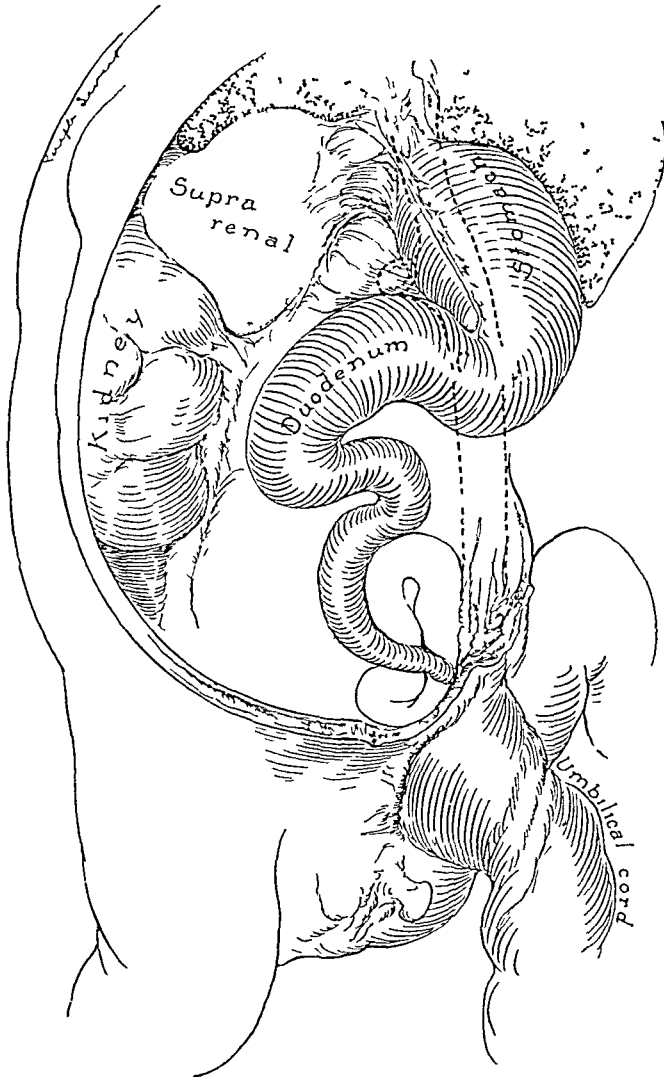


FIG 9—Dissection of a 13.5 Mm CR length embryo viewed from the right anterior aspect. The liver has been removed. The elongation and increase in size of the duodenum is extending into its second portion in the establishment of the secondary duodenal curves. The umbilical vein is indicated in dotted outline. The prearterial segment of the enterocolic loop is about to return into the abdominal cavity.

terminates by making a sudden flexure opposite the wolffian body (mesonephros). This flexure is the future duodenojejunal flexure. The duodenum as a whole is shaped rather like the letter U placed horizontally with its convexity ventrally and with the vitelline vein lying in its concavity. The second portion of the duodenum is extremely short and inclines a fraction to the right to enter the third and fourth portions, which are represented by little more than a slight curve at the future duodenojejunal junction. Under the

influence of the increase in size of the body cavity, the determination of the position of the stomach and the enlargement of the future portal vein, the essentials of the permanent curvature of the first portion of the duodenum have been established

Stage III —The Duodenal Loop, (Fig 9) The stage initiating the establishment of the duodenal loop and the attainment of its adult form is characterized by the very rapid development and elongation of the second portion of the duodenum and slightly later of the two succeeding parts. At this time, various observers (Tandler,⁴⁰ Johnson²⁰) have noted in the lower two-thirds

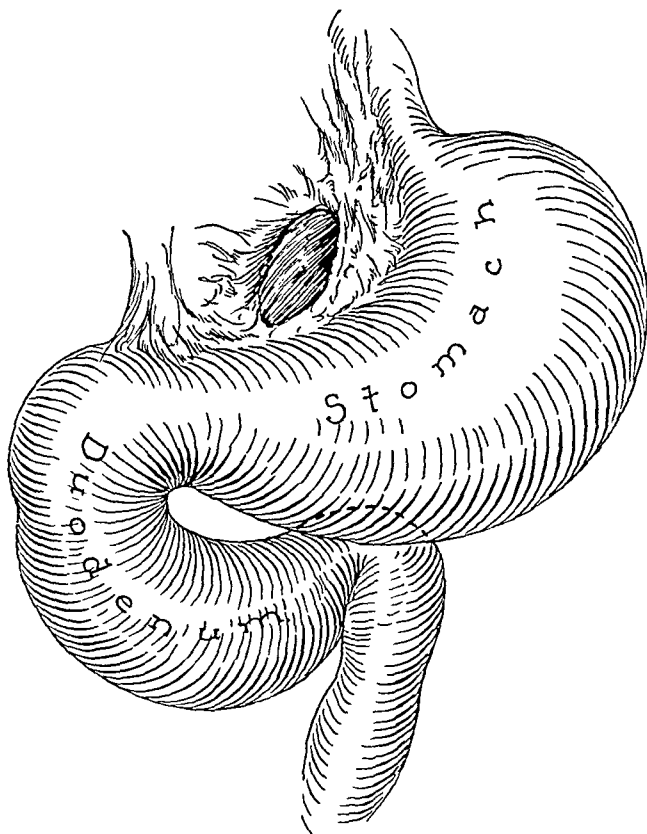


FIG 10 —Dissection of a 43 Mm CR length embryo. The enlargement and elongation of the duodenum has extended to the third and fourth portions. The duodenal loop still exceeds that of the jejunum in diameter. The duodenojejunal flexure has crossed to the left of the midline.

of the duodenum, overgrowth of the epithelial lining amounting to an actual occlusion of the duodenal lumen. Vacuolization follows, 22–24 Mm, leading to reestablishment of the lumen and formation of the villi. At 30 Mm, the vacuoles having coalesced, the lumen is pervious throughout. Differential growth has resulted in the elongation of the ligament of Treitz and the transference of the duodenojejunal flexure to the left of the midline (Fig 10). Hunter,¹⁷ in this connection, stresses the importance of the part played by fixation bands in the formation of the duodenal curve. Frazer,¹³ criticizing this view, believes that the curve is produced under the influence of the

growth of the head of the pancreas. We, however, do not subscribe to either of these views and regard the curvature of the duodenal loop as due to differential growth factors and time relationship rather than to mechanical effects.

Stage IV—Fixation The final stage concerns the ultimate placement of duodenojejunal flexure and fixation of the gut. The mesoduodenum has closely approximated the dorsal parietal peritoneum by the development of the pancreas between its layers, and fusion ensues. The adhesion is no doubt influenced by the returning gut. The transverse colon during the rotation of the extra-abdominal intestine is carried over the duodenum and adheres to it at the point of crossing.

The Genesis of Duodenal Anomalies—We have thought it advisable in view of the impossibility in the present state of our knowledge of making any definite statement as to ultimate cause, to relate the various errors in terms of the various stages of duodenal development previously discussed. In addition, certain general principles need emphasis. It should be recognized that such fundamental processes as growth and differentiation proceed independently of one another and may show varying velocities of change. There is ample evidence to show that the original control of differentiation appears to be exerted in relation to definite morphogenetic fields and is dependent, not upon any definite localization, but upon the position of any part relative to the whole structure or on the levels which the various parts occupy along an axis of development. It is perhaps safe to assert, judging from experimental evidence, that there are, for the alimentary tract, critical periods which precede differentiation and which differ in time in different parts of the gut. The ultimate effects produced in the way of errors are influenced by the relationship of the time of action of the noxious agent to the stage of differentiation attained.

Anomalies of the first stage are those associated with the development of the biliary and pancreatic rudiments resulting in such conditions as dichotomy of the bile duct and annular pancreas. In the former it is probable that the same influence that establishes the biliary anomaly is responsible for the associated atresia or stenosis of the duodenum. In the latter deformity any delay in the appearance of the ventral pancreatic rudiment from the duodenum is envisaged as forcing this portion of the pancreas to follow the further development of the duodenum rather than the dorsal rudiment. Both of these anomalies are regarded as having their origin in the earliest stages of development.

Anomalies of the second stage associated with the development of the first part of the duodenum are almost unknown. We have been unable to find records of a single instance of atresia or stenosis affecting this portion. Such freedom from error is not unexpected by virtue of the early establishment of this portion of the duodenum. Its development, closely associated with that of the stomach, shows an initial preponderance over the rest of the duodenum and in the formation of its essential curves (Fig. 8).

The third stage is of the greatest importance from the point of view of errors affecting the lumen and shape of the duodenum. As already pointed out, the formation of the second and third parts of the duodenum occurs comparatively late in development, and is characterized by a period of rapid elongation eventuating in the establishment of the adult form and shape (Fig 9). The majority of duodenal anomalies involve this portion of the gut. Any factor which interferes with this critical period of growth would lead to complete or partial obliteration of the lumen.

It would seem to us that the mechanism producing atresia, stenosis or valve formation is essentially the same, varying only in degree and in time.

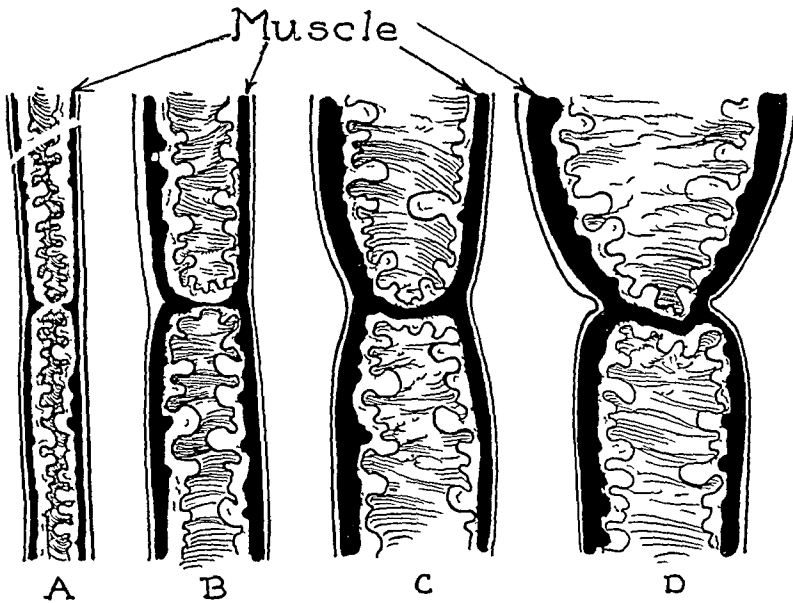


FIG. 11.—Illustrating the successive stages in the formation of a duodenal valve. Differential growth above and below the retarded area has produced the valve which therefore contains muscle between the two layers of epithelium.

of genesis. In addition, such retardation, particularly if extensive, must secondarily bring about distortion of the duodenal loop, as is so commonly found. Atresia is regarded as the result of early retardation. The same factor acting a little later would result in stenosis rather than atresia with less disturbance of the duodenal loop (Case 1). If the disturbance affects a very limited segment of the gut, differential growth above and below the point of interference would result in the formation of a valve (Fig 11). Such a mechanism would account for the otherwise unexplained presence of muscular tissues in such septa as in Case 2. The presence or absence of septal perforation and its size may, apart from the possibility of secondary perforation, be related to the time of retardation, during, before or after the establishment of a lumen.

We regard the rapid elongation of the second and third portions as being responsible for the opening out of the duodenal loop. Anomalies of shape or retention of the primitive curve as in the duodenum in "M" may result from premature elongation before the requisite amount of space is

available for its reception or from the influence of neighboring organs such as an excessively large liver (Case 3) or premature return of the umbilical loop.

Errors of the fourth stage are the result of failure of peritoneal fixation. In themselves they are of little importance excepting insofar as they may allow of kinking of the bowel or be associated with abnormalities of rotation affecting the remaining intestine. Errors of fixation are commonly associated with obstruction of the lumen. In Case 1 a free duodenum was associated with stenosis, nonrotation of the gut, together with persistence of a hepato-duodenocolic ligament.

Diagnosis—The past decade has added little to our store of knowledge with regard to the early diagnosis of congenital duodenal obstruction, whether due to stenosis or atresia. Ladd,³⁰ in a recent paper, again stresses the fact that duodenal obstruction will give the signs common to high intestinal obstruction. He emphasizes the importance of upper abdominal distention, visible reverse gastric peristalsis, the presence of dehydration and shock and the laboratory findings of ketosis. The afore-mentioned signs are common to all high bowel obstructions. It should be emphasized at this point that children with true hypertrophic pyloric stenosis do not vomit until the seventh or ninth day at the earliest, whereas those infants with duodenal obstructions vomit as early as the first 24 hours. Fairber,¹² some five years ago, emphasized the fact that the absence of cornified epithelial cells in the meconium was proof that an atresia existed somewhere along the length of the gastrointestinal tract. He has developed a specific stain for these cells and both he and Ladd³⁰ have found that this test is of value in diagnosis. Most writers agree that hematemesis and the presence of coffee-ground vomitus in the absence of a blood dyscrasia, is a pathognomonic sign of duodenal atresia, most authors giving figures as high as from 65 to 85 per cent of all cases having this finding. Absolute constipation is the rule, but some cases pass what appears to be a true stool. Icterus of moderate degree is present in a good number of cases. One should not be misled as to the site of the atresia by the presence of bile pigments in the stool, as authors have stressed the fact that the presence of accessory biliary ducts emptying below the obstruction are not at all uncommon. The roentgenogram is, of course, of considerable value, the presence of a large gas bubble in the stomach and its site of termination often helping to confirm the diagnosis. Most surgeons attempt to corroborate their diagnosis by the giving of a small amount of barium by mouth. We feel that a warning should be posted with regard to this procedure if a later short circuiting operation is to be carried out. This warning is necessary because it has been found that the barium will often plug the anastomotic stoma, with subsequent obstruction. If barium is used it should be followed by a thorough washing out of the stomach and upper duodenum to prevent this catastrophe.

Treatment—The treatment of congenital duodenal obstruction is essentially surgical and should be instituted at the earliest possible time compatible

with the physical condition of the infant. It is unnecessary to discuss the actual surgical procedures to be employed, except to point out that because of the smallness of the bowel in infancy, they are often attended by considerable technical difficulty. To overcome these difficulties two points with regard to surgical treatment are of special interest and deserve emphasis. The extreme contraction of the distal segment for anastomosis is one of the prime causes of trouble in performing the operative procedure and is responsible for the large percentage of postoperative complications. Clogg,⁷ as early as 1904, and Wangenstein,⁴² in 1931, have emphasized the importance of ballooning up the distal segment by means of hydrostatic pressure. This maneuver has the double advantage of increasing the size of the distal segment, thereby making it more amenable for anastomosis, and also testing the patency of the bowel lumen distal to the area of obstruction, often indicating other constrictions at lower levels which necessarily would alter the plan of procedure. Multiple constrictions are relatively common. The final point of interest, from a technical standpoint, regards the use of extremely fine silk or linen as a suture material, and the performance of the anastomosis with a single anterior and posterior layer to obviate narrowing of the lumen. It has been found that this technic rewards its user with a higher percentage of successful results. We feel that the early diagnosis of these conditions combined with prompt surgical procedure will bear fruit in giving a higher percentage of cures. A thorough knowledge of the developmental anatomy of the duodenum is essential to the diagnostic and therapeutic problems involved in the treatment of these conditions. It is perhaps the rarity of congenital obstructions which is responsible, more than anything else, for the poor prognosis in the majority of cases reported and for the relative therapeutic inertia.

SUMMARY

- (1) Three cases of congenital duodenal malformation are reported.
- (2) The literature and etiologic hypotheses are briefly discussed.
- (3) The development of the duodenum, as observed from the microscopic dissections, is given as a basis for the classification and opinions on the genesis of these anomalies.
- (4) A brief outline of diagnosis and treatment is given.

We wish to acknowledge with thanks the courtesy of the Division of Surgery, Dr Jacob Smith for Case 2, for Case 3, Dr Francis S. Smyth of the Division of Pediatrics, and Dr Parry Douglas for referring Case 1.

BIBLIOGRAPHY

- ¹ Anderson, J. H. Abnormalities of the Duodenum. *Brit Jour Surg*, 10, 316-321, 1922-1923.
- ² Anderson, W. W. Congenital Atresia of the Colon in a Newborn. *Jour Med Assoc Georgia*, 21, 483, 1932.
- ³ Bauer, G. Störung der Entwicklungsmechanik der Darmdrehung unter Einfluss einer Darmstenose. *Centralbl f allg Path u path Anat*, 63, 193-199, 1935.

- Bland-Sutton, J See No 39, Sutton, J Bland
- ⁴ Bonar, T G D Congenital Atresia of the Duodenum *Lancet*, 7, 822-824, 1935
- ⁵ Breton, M Anomalies Duodinales *La Presse Med*, 42, 627, 1934
- ⁶ Cautley, E Duodenal Stenosis *Brit Jour Children's Dis*, 16, 65-73, 1919
- ⁷ Clogg, H S Congenital Intestinal Atresia *Lancet*, 2, 1904, 1770-1774
- ⁸ Cordes, L Congenital Occlusion of the Duodenum *Arch Pediat*, 18, 401-424, 1901
- ⁹ Davis, D M, and Poynter, C W M Congenital Occlusion of the Intestines, with Report of a Case of Multiple Atresia of the Jejunum *Surg, Gynec, and Obst*, 34, 35-41, 1922
- ¹⁰ Del Campo, R M La oclusion aguda en el recién nacido *Archives Uruguayos de medicina y cirugía*, 1, 237-245, 1932
- ¹¹ Ernst, N P A Case of Congenital Atresia of the Duodenum Treated Successfully by Operation *Brit Med Jour*, 1, 644-645, 1916
- ¹² Farber, S Congenital Atresia of the Alimentary Tract *J A M A*, 100, 1753-1754, 1933
- ¹³ Frazer, J E Note on Doctor Hunter's paper on Development of the Duodenum *Jour Anat*, 61, 356-359, 1926-1927
- ¹⁴ Freeman, L A Congenital Anomaly of the Duodenum and Its Surgical Significance *Surg, Gynec, and Obstet*, 30, 454-456, 1920
- ¹⁵ Garvin, J A Congenital Occlusion of Duodenum by a Complete Diaphragm *Am Jour Dis Chil*, 35, 109-112, 1928
- ¹⁶ Harris, M L Constrictions of the Duodenum Due to Abnormal Folds of the Anterior Mesogastrium *J A M A*, 62, 1211-1215, 1914
- ¹⁷ Hunter, R H A Contribution to the Development of the Duodenum *Jour Anat*, 61, 206-212, 1926-1927
- ¹⁸ Jackson, R H Congenital Constriction of the Duodenum Due to an Abnormal Fold of the Anterior Mesogastrium *ANNALS OF SURGERY*, 84, 723-728, 1926
- ¹⁹ Jewesbury, R C, and Page, M Two Cases of Duodenal Obstruction Treated by Operation *Proc Roy Soc Med*, 16, 1, 50-54, 1923
- ²⁰ Johnson, F P The Development of the Mucous Membrane of the Œsophagus, Stomach and Small Intestine in the Human Embryo *Amer Jour Anat*, 10, 521-561, 1910
- ²¹ Jones, T B, and Morton, J J Congenital Malformations of the Intestine in Children *Amer Jour Surg*, 39, 382-399, 1938
- ²² Judd, E S, and White, R B Congenital Anomalies of the Duodenum *ANNALS OF SURGERY*, 89, 1-5, 1929
- ²³ Kaldor, J Atresia of the Duodenum and Duodenal Diverticula *ANNALS OF SURGERY*, 89, 6-10, 1929
- ²⁴ Keith, A A Demonstration of Constrictions and Occlusions of the Alimentary Tract of Congenital or Obscure Origin *Brit Med Jour*, 1, 301-305, 1910
- ²⁵ Kelley, J F Partial Intestinal Obstruction Due to Congenital Anomaly of the Duodenum, and Partial Rotation of the Colon *Amer Jour Surg*, 22, 299-302, 1933
- ²⁶ Kellogg, E L, and Collins, J T Congenital Duodenal Obstruction *Amer Jour Surg*, 30, 369-371, 1935
- ²⁷ Kreuter, E Die angeborenen Verschlüssungen und Verengerungen des Darmkanals im Lichte der Entwicklungsgeschichte *Deutsch Ztschr f Chir*, 79, 7-89, 1905
- ²⁸ Kreuter, E Zur Aetiologie der congenitalen Atresien des Darms und Oesophagus *Arch f klin Chir*, 88, 303-309, 1909
- ²⁹ Kuliga, P Zur Genese der congenitalen Dunndarmstenosen und Atresien *Beitr z path Anat u z allge Path*, 33,, 481, 1903
- ³⁰ Ladd, W E Congenital Obstruction of the Small Intestine *J A M A*, 101, 1453-1458, 1933
- ³¹ Mangos, W F, and Clerf, L H Congenital Anomalies of the Alimentary Tract with Special Reference to the Congenitally Short Oesophagus *Amer Jour Roentgen*, 33, 657-669, 1935

- ³² Metcalfe, R F Report of a Rare Congenital Malformation of Intestine Amer Jour Surg, 21, 294-296, 1933
- ³³ Moritz, A R Development Anomalies Causing or Predisposing to Intestinal Obstruction Ohio State Med Jour, 30, 429-433, 1934
- ³⁴ Nat B S, and Mookerji, P O Abnormal Duodenum Jour Anat, 64, 250-253, 1929-1930
- ³⁵ Odgers, P N B Some Observations of the Development of the Ventral Pancreas in Man Jour Anat, 65, 1-7, 1930-1931
- ³⁶ Rocher, H L, Rondil, G, and Couriades, J Stenose duodenale par malformation du pedicule hepatique Ann d'Anat Pathol, 10, 277-285, 1933
- ³⁷ Seidlun, S M Congenital Duodenal Septum with Obstruction Bull Johns Hopkins Hosp, 37, 328-339, 1925
- ³⁸ Spriggs, N I Congenital Intestinal Occlusion Guy's Hosp Rep, 66, 143-218, 1912
- ³⁹ Sutton, J Bland Imperforate Ileum Amer Jour Med Sci, 98, 457-462, 1889
- ⁴⁰ Tandler, J Zur Entwicklungsgeschichte des menschlichen Duodenum in fruhen Embryonalstadien Morph Jahrb, 29, 187-216, 1901
- ⁴¹ Theremin, E Uber congenitale Occlusionen des Dunndarms Deutsch Ztschr f Chir, 8, 43-71, 1877
- ⁴² Wangenstein, O H Diagnosis and Treatment of Acute Intestinal Obstruction Northwest Med, 30, 389-407, 1931

FURTHER OBSERVATIONS ON THE DIAGNOSIS AND TREATMENT OF GASTRIC LESIONS

CRANSTON W. HOLMAN, M.D.

AND

WILLIAM R. SANDUSKY, M.D.

NEW YORK, N. Y.

FROM THE DEPARTMENT OF SURGERY, NEW YORK HOSPITAL AND CORNELL UNIVERSITY MEDICAL COLLEGE, NEW YORK, N. Y.

A RECENT REVIEW of the patients who were operated upon in the New York Hospital for ulcer and carcinoma of the stomach has again emphasized the difficulty of establishing a correct diagnosis of lesions of the stomach. The investigations of Bloomfield and his associates^{2, 3} of the gastric secretion have led to a better understanding of the physiology of the stomach in health and disease, and, again, have called attention to the value of gastric analysis as an aid in the correct diagnosis of gastroduodenal lesions. Their findings were corroborated by a similar study,¹ which also pointed out the difficulties experienced by the surgeon in establishing a diagnosis even when the lesion was actually visualized and palpated.

These papers dealt with lesions of the duodenum as well as of the stomach. However, since only gastric lesions present a problem in surgical therapy, so far as malignancy is concerned, it was thought that a study confined strictly to the problem of the differential diagnosis of ulcer and carcinoma of the stomach would be of value, particularly in determining the proper surgical therapy. The result of this study shows that in many instances a correct diagnosis cannot be established by any of our present methods, and is strong evidence in favor of the attitude of removal of all gastric lesions, if feasible, when surgical therapy is undertaken.

This report is based upon the findings in 53 patients with ulcer of the stomach and 104 patients with carcinoma of the stomach, who were studied thoroughly, operated upon, and followed postoperatively.

The problem of the diagnosis of gastric ulcer can best be demonstrated by referring to Chart 1, in which the comparative value of various diagnostic procedures in establishing a correct diagnosis is shown. The outstanding fact revealed is that all benign ulcers, so far investigated, have had an acidity that was normal or above normal (60 per cent free hydrochloric acid or more). During the same period 155 patients with proved duodenal ulcers were also studied, all of whom had acidities of 60 degrees or more of free hydrochloric acid.

Chart 2 lists the comparative value of the various diagnostic procedures in the correct diagnosis of carcinoma of the stomach. It will be seen that approximately a 15 per cent error in diagnosis can be expected from any

Submitted for publication May 3, 1939

one of the diagnostic procedures. Fortunately, when all the accumulated evidence is weighed, the error in diagnosis is considerably decreased.

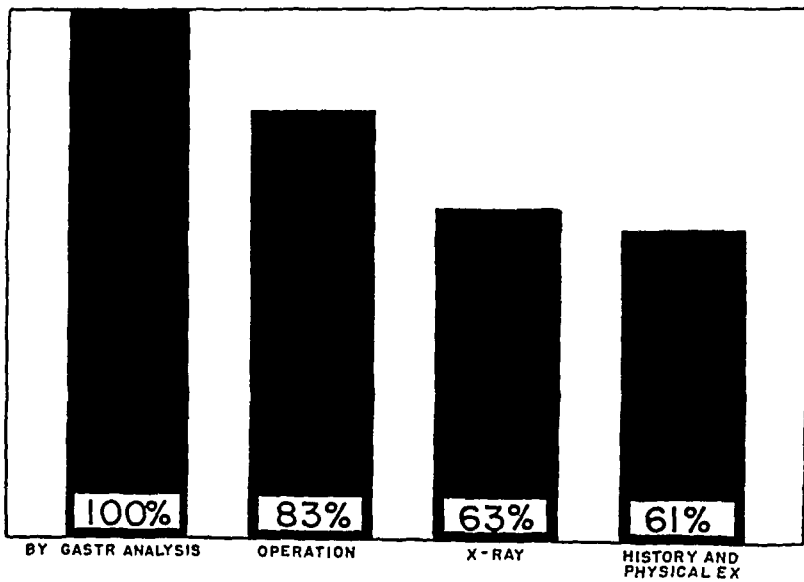


CHART 1—Percentage of correct diagnoses in gastric ulcer

In Chart 3 is shown the comparative value of the various diagnostic procedures in all patients with gastric lesions (ulcer 53, carcinoma 104). As appears in this chart, all available methods fail to establish a diagnosis in a certain percentage of patients. For clarity in discussion we shall consider the data in this chart separately.

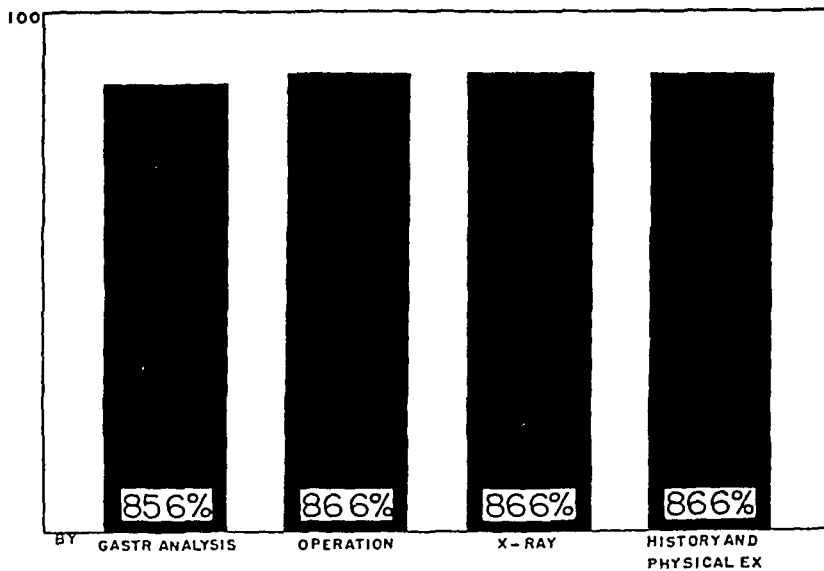


CHART 2—Percentage of correct diagnoses in carcinoma

History and Physical Examination—The character and the duration of the symptoms and the age of the patient vary so greatly in ulcer and cancer that their practical value in establishing a diagnosis is minimal. Of

GASTRIC LESIONS

greatest value is the presence of a palpable mass, which almost always signifies malignancy. Unfortunately, it is in those patients in whom the diagnosis is doubtful—whether cases of early cancer, cancerous ulcer, or ulcer—that a mass is rarely palpable. In spite of the difficulties in the differential diagnosis between ulcer and carcinoma of the stomach, a careful history and physical examination established a correct diagnosis in 61 per cent of the cases of ulcer and in 86 per cent of the cases of carcinoma.

Roentgenologic Examination—In spite of improvements in the technique of fluoroscopy and roentgenography, the differentiation between gastric ulcer and carcinoma was not possible in 33 of 157 patients subjected to roentgenologic and fluoroscopic studies. To be sure, in the majority of instances the roentgenologist did not diagnose the lesion incorrectly, but merely stated

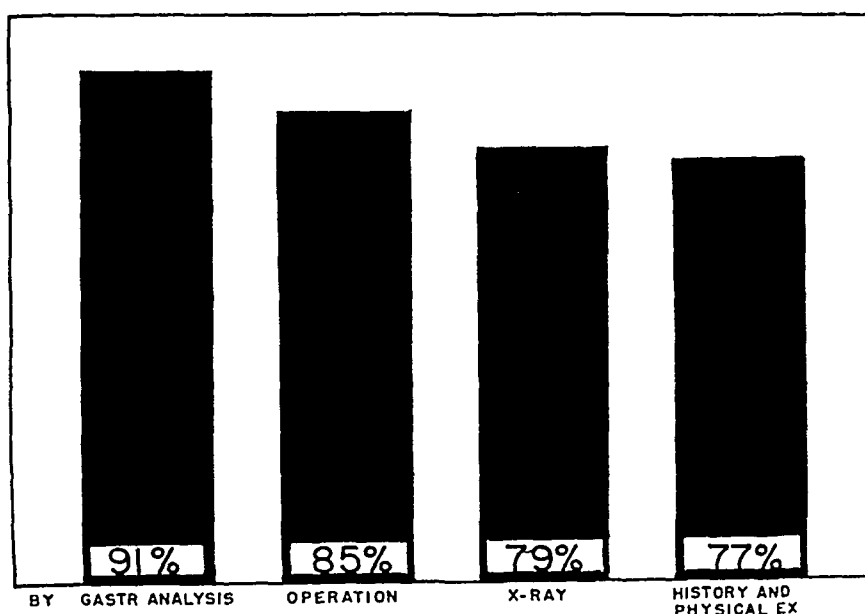


CHART 3—Percentage of correct diagnoses in lesions (ulcer and carcinoma) of the stomach

his inability to say definitely whether ulcer or carcinoma was present. Nevertheless, the expression of doubt by the roentgenologist in these 33 patients diminishes, for the surgeon, the value of the roentgenograms in determining the nature of the lesion.

Gastric Analysis—Anacidity or hypo-acidity has been said to be the best evidence in favor of the presence of malignancy, and, conversely, hyperacidity to be the best evidence of benign lesions. In 15 of the 157 cases, the gastric analysis favored a diagnosis which proved to be incorrect. All these failures occurred in patients with carcinoma (104) who had 60 degrees or more of free hydrochloric acid, thus, approximately 15 per cent of patients with carcinoma have considerable acid. However, as a low acidity or an anacidity has never been found in a benign lesion, the best single evidence of malignancy is a low gastric acidity. This statement can be made only if a careful analysis, according to the method of Bloomfield and Pollard,² is made by someone who is interested in establishing the correct diagnosis. As shown

in Chart 3, the diagnosis was correct in a larger percentage of cases when it was based on the gastric analysis than when any other *single* method was relied upon

Operative Diagnosis—In no other part of the body do the processes of inflammation and malignancy assume such similar characteristics as they do in the stomach. In 23 of the 157 patients, the operator was unable to determine at operation, with the lesion under direct vision and palpation, whether the process was malignant or benign. In several instances an incorrect diagnosis was made. Although the majority of these patients were not operated upon by us, we had the opportunity of discussing with the surgeon his opinion and his diagnosis before he was influenced by the pathologic reports of the specimens removed.

Discussion—First, it must be made clear that this discussion deals only with those patients in whom operative interference, for one reason or another, is contemplated. We are not suggesting rules for the treatment of all gastric ulcers, but are limiting our remarks to a consideration of the operation of choice for those patients who are about to be subjected to surgical therapy. (For discussions of the medical approach to this problem, the reader is referred to the papers of Bloomfield³ and Comfoit and Van Zant⁴.) An important factor in determining the procedure of choice is whether the lesion is benign or malignant. With the exception of a low acidity or an acidity, which, when reliably determined, must be considered as an indication of malignancy, the fallibility of preoperative diagnostic criteria in the individual case is so great that their value as reliable aids is compromised, and since there is a possibility of error in diagnosis even with the lesion visible and palpable, it would seem that the treatment of choice is removal. However, considerations other than the probability of malignancy may influence the selection of a given procedure, namely, the condition of the patient, the feasibility of removal, the accessibility of the lesion, and the presence of metastases. The argument against partial gastric resection—whether wide excision or resection—because of the operative mortality, is not supported by the results in this group of patients. On 47 patients wide excisions or partial resections were performed, with three deaths, a mortality of 6.3 per cent. In conclusion it may be said that the attitude favoring removal of lesions of the stomach, when feasible, gains considerable support when confirmed by investigations on a thoroughly studied group of patients.

CONCLUSION

In summarizing, a low acidity or an acidity, determined by a reliable method, remains the single most reliable evidence of carcinoma. Since approximately 15 per cent of carcinoma are associated with considerable acid, and since all methods of diagnosis, including operative exploration, are fallible in some patients, it would seem that, when feasible, the operative therapy of choice is wide excision of the lesion or gastric resection.

REFERENCES

- ¹ Holman, Cranston W The Diagnosis of Gastric Carcinoma and Peptic Ulcer
 J A M A , 108, 1383, April 24, 1937
- ² Bloomfield, A L , and Pollard, W S The Diagnostic Value of Studies of Gastric
 Secretion J A M A , 92, 1508, May 4, 1929
- ³ Bloomfield, A L The Diagnosis of Early Cancerous Changes in Peptic Ulcer
 J A M A , 104, 1197, April 6, 1935
- ⁴ Comfort, M W , and Van Zant, F R Gastric Acidity in Carcinoma of the Stomach
 Am Jour Surg , 26, 447, December, 1934

RETROGRADE ENTERIC INTUSSUSCEPTION

MORRIS J. GROPER, M.D.

SAN FRANCISCO, CALIF.

RETROGRADE INTUSSUSCEPTION is a surgical entity that is infrequently seen and less often considered. Retrograde intussusception may involve any portion of the gastro-intestinal tract from the sigmoid to the stomach. In a study of the literature on this subject it is noticeable that reports of intussusception, both of the isoperistaltic and the retrograde type, have markedly increased during the past decade. It is my intention to suggest a classification and to discuss the etiology and mechanics of intussusception. The case which is herewith reported is of the enteric type and involved the ileum and jejunum.

Classification of Retrograde Intussusception—A classification of the pathologic process along anatomic lines appears most logical. (1) Jejuno-gastric—the jejunum prolapsing through the gastrojejunostomy stoma, (2) enteric—the jejunum or ileum being involved, (3) ceco-ileal—the cecum prolapsing into the terminal ileum, (4) colic—any portion of the large bowel invaginating a more proximal part.

Numerous cases of retrograde intussusception of the jejunum as a complication of gastro-enterostomy have been noted. This is a serious sequela that may occur many years after the initial operation and may result fatally unless diagnosed early. Bettman and Baldwin⁵ reviewed the literature up to 1933, and found 33 cases similar to the one they reported. Adams¹ and Debenham¹⁰ both reported cases of retrograde jejuno-gastric intussusception with recovery. Becker⁴ records a similar case in which the intussusceptum measured 18 inches.

Cioffi⁸ and Caminiti⁷ each reported a case of retrograde intussusception involving the small intestine. The former was due to a Meckel's diverticulum while the latter was due to an angio-adenoma. Todyo,²¹ in reviewing 154 cases of intussusception, stated that he had seen three of the retrograde type. One of them was retrograde, multiple, superimposed and recurrent. Buckley⁶ operated upon a child, age two, that showed a superimposition of a retrograde upon a direct intussusception of the small intestine. D'Aicy Power,¹⁷ in 1899, wrote several accounts of the usual type of intussusception as well as accounts of his experience with two cases of the retrograde type. Clubbe,⁹ in his volume on the diagnosis and treatment of intussusception, describes a combined case of simple and retrograde intussusception. Goodyear¹³ reported one of the most interesting cases, in which he found a retrograde intussusception of the cecum into the terminal ileum. Lewis¹⁵ reported a case of retrograde intussusception of the pelvic and descending colon into the transverse colon with the apex of the intussusception at the cecum. Romanis and Mit-

chiner,¹⁰ in their text-book of surgery, record one case of retrograde intussusception in the colon of a living patient. Flemming¹² successfully operated upon an intussusception of the descending colon into the transverse colon, the etiologic factor being a benign polyp. In a study of 1,000 cases of intussusception, Fitzwilliams¹¹ reports six cases of the retrograde type. In one of them the descending colon was invaginated into the transverse colon. Schoenfeld²⁰ reported the retrograde intussusception of the sigmoid into the descending colon in a child, age four months.

Etiology and Mechanics of Intussusception—The etiology of intussusception is still a moot question. In many instances the causal agent is evident, but in numerous instances the exact nature of the process and its inception remain a debatable problem. Perrin and Lindsay¹⁶ wrote a monograph based on a study of 400 cases. They stated that 78.5 per cent of all acute intussusceptions occur in children under two years of age. In their series they had two cases of retrograde intussusception. The following causes of intussusception were listed by them for consideration: (1) Perverted peristalsis, (2) a paralytic condition of the intestine which allowed the prolapse of one portion into another, (3) the presence of some congenital abnormality such as a constriction, or new growth such as a carcinoma, acting as the precipitating cause. They offer for further consideration the theory that the swelling of preexisting lymphoid tissue, which is especially prominent in the ileocecal region, may provoke an intussusception. In very young children gastrointestinal disturbances are quite common. When these two factors are combined, it is possible to conceive of an ileocecal or ileocolic intussusception occurring. Strong catharsis must be considered in this connection as an additional factor.

Fitzwilliams¹¹ brings out a point which is worthy of emphasis. He believes that the apex of an intussusception is fixed and does not change. During the process of invagination the apex remains as a fixed point. In discussing the mechanism further, he feels that slight intussusceptions probably form frequently but their dissolution is physiologic. In a small minority of cases it goes further. A local constriction becoming overlapped by the dilated bowel below to such an extent that it can be grasped by the latter is all that is needed to initiate an intussusception. There is a fine line between the physiologic and pathologic, and at times some small factor turns the scales.

Balfour³ has been fortunate in actually observing the mechanism of retrograde intussusception at the operating table. In an operation for obstruction due to a tumor at the sigmoid he noted that there was a retrograde intussusception of the sigmoid into the descending colon. The intussusception was reduced but as he watched the area, strong antiperistaltic activity set in and it invaginated itself again. Balfour felt that retrograde intussusception of the small intestine was an impossibility. He believes that normally there may be in the large intestine antiperistaltic contractions but does not feel that this holds true of the small intestine. He, therefore, holds that retrograde intussusception may not occur in the latter. If it does it is a terminal event.

associated with simple intussusception or with the reverse peristalsis of obstruction. In reviewing the literature numerous writers quote from Lockhart-Mummery who states emphatically in his text-book "Retrograde intussusceptions do occur but only during death or as a result of asphyxia, they are not met with in practice." This belief is contradicted by the numerous case reports in the literature of retrograde intussusception of the small intestine in the living patient. The mechanism involved is essentially the same as in the ordinary case of intussusception. Instead of having increased normal peristalsis, the neuromuscular mechanism is thrown into reverse so that forceful antiperistalsis is provoked. Alvarez² devotes an entire chapter to the subject of reverse peristalsis. He cites numerous incidents wherein drugs administered rectally were vomited some hours later. The fecal vomiting of ileus is a classic example of the reversal of normal activity.

Treatment of Intussusception—We have traveled a long way in the matter of therapy when we consider an article written by Langstaff,¹⁴ in 1807, in which he reports a case of intussusception which ended fatally in a child, age four. He concludes "At the same time that we recognize the inefficacy of art, these cases will teach us to repose a just confidence in the powers of nature, and to retain some hope of a favorable event under the most unpromising circumstances." Langstaff preferred to take the chance of letting the intussusceptum slough with the hope that there would be a reestablishment of the continuity of the bowel. This undoubtedly does occur since I have seen one such case in which the diagnosis was not made until after the intussusceptum sloughed and was passed per rectum. In this instance the intussusception involved the transverse and descending colon. The patient made a spontaneous recovery.

In many cases, especially in children, reduction of the intussusception has been accomplished by the use of the barium enema. However, in considering the matter of retrograde intussusception involving the large intestine, the use of the barium enema is contraindicated since all that would be accomplished would be an increase in the size of the intussusception with an aggravation of symptoms. The treatment is early and adequate surgery. The procedure to be employed will depend on the causal agent and the condition found at operation. The following case of retrograde enteric intussusception complicated by volvulus is an example of the difficulties encountered in diagnosis and the radical therapy which may be required.

Case Report—H. R., white, female, age 69, unmarried, was seen at 7 A. M., December 29, 1938, and stated that she had been seized with a sudden, severe, spasmodic, epigastric pain, which caused her to cry out in distress. The sharp pain continued to come and go at intervals and she had continued to have a constant residual dull ache limited solely to the epigastric region. There was no radiation of pain. She was nauseated frequently and had vomited twice. Her bowels had moved that morning and there was no blood noted either in the stool or in the vomitus. Morphine sulphate was administered twice within a period of one hour with only moderate relief. She stated that she had suffered with similar episodes over a period of one and one-half years, none of these had

approached the severity of the present attack. These attacks would appear at intervals of five or six weeks and last several hours. Her last attack was five days prior to the present one.

Previous History—Patient had been active up to ten years ago. She had had measles, mumps, whooping cough and chickenpox. There was no history of diphtheria, typhoid fever or rheumatic fever. Her tonsils and a small lipoma were removed during her childhood.

There was no history of clay-colored or tarry stools, jaundice or food intolerance. Aside from obesity she had occasional ankle edema, dyspnea on exertion, and mild arthritis. One year ago, a gastric analysis showed an anacidity, for which she had been taking 20 minims of hydrochloric acid three times a day. Ten years ago, because of easy fatigue, a basal metabolism was taken and showed -20 . She had been taking thyroid to correct this deficiency. At that time she weighed 207 pounds. Her present weight was 190 pounds. Her menopause had occurred at the age of 40.

Physical Examination—December 29, 1938. The patient was a well developed, obese woman who appeared younger than her stated age. She looked moderately well and did not appear to be in much pain. Temperature 99.2° F. Pulse 70. Respirations 16. The heart sounds were good, with occasional extra systole. B P 150/80. The abdomen appeared normal in contour. No masses were seen. Palpation revealed a perfectly soft abdomen with a suggestion of tenderness in the epigastric region. There was a mass about the size of a grapefruit present in the left lower quadrant which was movable and not tender. She stated that she had been unaware of the presence of this mass. An examination by another physician, two weeks previously, had not revealed any mass.

Urinalysis showed a slight trace of albumin with a few hyaline casts. There were 2-4 R B C and 3-4 W B C per high power field. Hemoglobin 86 per cent, R B C 4,410,000. W B C 12,500, with 91 per cent neutrophils and 9 per cent lymphocytes.

Physical Examination—December 29, 1938. The general condition of the patient remained about the same throughout the day. She was still having paroxysms of pain referred to the epigastric region but they had become less severe. She continued to be nauseated. Examination of the abdomen revealed it to be distended, especially in the left lower quadrant. It moved freely with respiration. Palpation revealed a soft abdomen. No guarding or rigidity was present. Slight tenderness was noted in the epigastric region in the midline. A large, firm, nontender, ballotable mass filled the left lower quadrant and extended two fingers breadth above the umbilicus. It had increased materially since the earlier examination. It measured 24 cm in length and 17 cm in breadth. It could be grasped between the hands with ease and cause the patient no distress. The tumor was flat to percussion while the rest of the abdomen was tympanic. W B C 11,200, with 95 per cent neutrophils and 5 per cent lymphocytes. Stool examination was negative for occult blood.

Röntgenologic—Dr. A. Petrilli, San Francisco. A P abdominal film. "The right kidney is readily outlined opposite the 11th and 12th dorsal and first two lumbar vertebrae. The outline of the left kidney is not definitely seen although its lower pole is suggested at approximately the same level. The right kidney appears approximately normal in size, shape and position. The general G I tract is unusually free of gas. Two loops of bowel containing air are seen in the left upper quadrant but it is impossible to state definitely whether these are large or small bowel. Overlying the middle of the abdomen, from the 4th lumbar vertebra to the pelvis and extending to the flanks, is a large, lobulated, soft tissue mass with smooth margins. This mass contains no air. The extension on the right side reaches to the flank but on the left it lies several centimeters from the flank. Inferiorly, it reaches the upper margin of the distended urinary bladder. The spine shows degenerative arthritic changes especially between the 4th and 5th lumbar vertebrae where the disk-space is narrowed more on the left side and there is some evidence of rupture of the nucleus pulposus. Heavy lips of bone project from the lateral margins of

these two vertebrae (Fig 1) *Roentgenologic Diagnosis* Intra-abdominal mass, degenerative arthritis" *Preoperative Diagnosis* Acute intra-abdominal pathology, possibly a twisted ovarian cyst

Operation—Under spinal anesthesia, the abdomen was opened. There was no free fluid present in the peritoneal cavity. Several large, markedly distended, hemorrhagic and apparently gangrenous loops of bowel presented themselves. They were so apposed and adherent to each other that they gave one the impression on palpation of being a single rounded mass. The loops of bowel were gradually oriented so that it was apparent that we were dealing with a retrograde intussusception of the ileum into the ileum and jejunum as well as a volvulus at the site of intussusception. Neither the



FIG 1—Roentgenogram, taken three hours before operation showing large, soft tissue mass filling the lower abdomen. The mass outlined by dotted line, consists of obstructed bowel containing no gas.



FIG 2—Ileum showing multiple polypi within the lumen. (A portion of the tumor has been removed for section.)

volvulus nor the intussusception could be reduced because of the extensive edema present in the bowel and mesentery. It was obvious that a resection was necessary. Seven and one-half feet of jejunum and ileum were resected and a side-to-side anastomosis performed. On opening the distal segment of bowel a small, isolated, mucosal polyp was noted. It measured approximately 2 cm in height and 1.5 cm at the base. It was removed for examination. The abdomen was closed without drainage. Silver wire was used as through-and-through retention sutures. Fifteen thousand units of polyanerobic antitoxin (Cutter) was administered intramuscularly.

Pathologic Examination—Gross Dr P. M. Smith, San Francisco. "The specimen (Fig 2) consists of approximately seven and one-half feet of small intestine, apparently it includes a small part of the jejunum, but is mostly proximal ileum. The proximal and distal two inches are pale red, the remainder is deep purplish-red and is markedly dilated, approximately 10 cm in circumference. The mucous surface is dull red. Four point five centimeters from the proximal end, there is an abrupt line of demarcation, proximal to which the mucosa is pale and has its normal lustre. At the border of the discolored

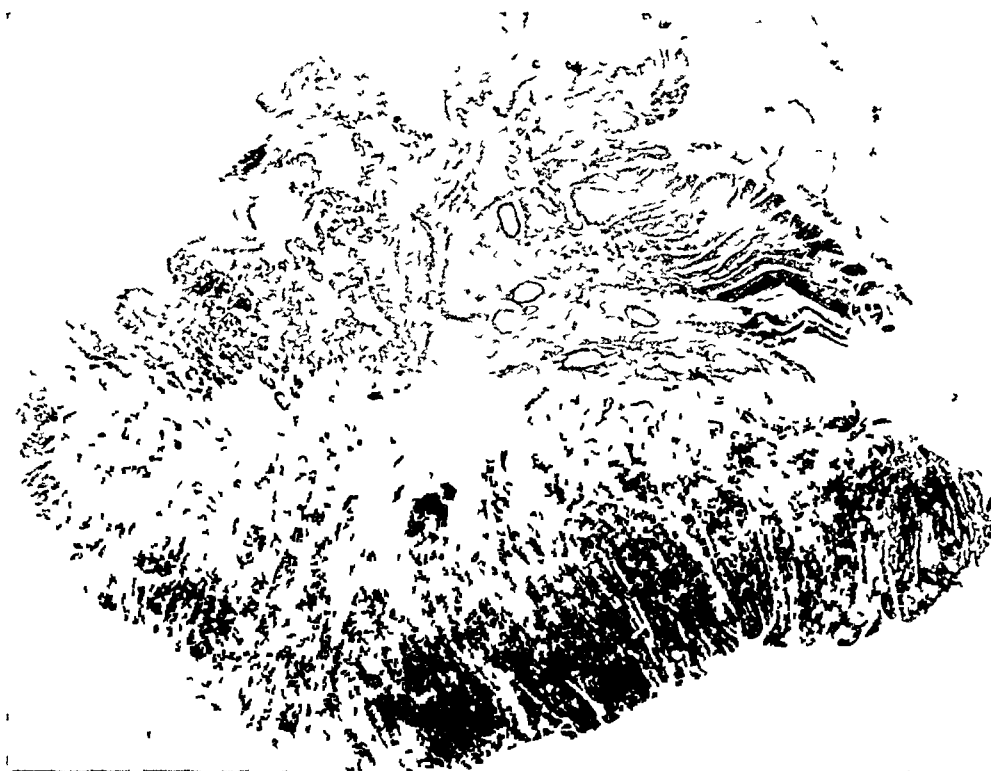


FIG 3—Photomicrograph of a portion of the tumor showing polyp formation
(Low power)



FIG 4—Photomicrograph of the polyp the villi are markedly elongated with the submucosa increased in thickness. The tissue is edematous, with the capillaries and veins dilated and filled with blood.
(High power)

portion there is a large, irregular, flattened polypoid mass 6x6 cm in size. The underlying wall does not seem to be infiltrated. A portion of the mesentery is markedly thickened, edematous and slightly congested. There are no thrombi in the vessels. An additional specimen measuring 15x1x0.5 cm was removed from an adjacent loop of the ileum. It is partly covered by yellowish membrane."

Microscopic "In sections from the purplish area, the tissues are edematous and the capillaries and veins are dilated and filled with blood. Many of the epithelial cells are exfoliated and their nuclei are pyknotic, but there is no loss of nuclear staining. In the polypoid masses in both the jejunum and ileum, the villi are markedly elongated and the submucosa is increased in thickness (Figs 3 and 4)." *Pathologic Diagnosis* "Segment of jejunum and proximal ileum showing marked edema, passive congestion and dilatation. Benign mucous polypi, jejunum and ileum."

Postoperative Course—The patient had an uneventful convalescence, her wound healing per primam. She was given three small transfusions of 250, 200, and 350 cc, and was discharged, January 26, 1939.

CONCLUSIONS

(1) A case of retrograde enteric intussusception associated with volvulus is presented.

(2) Retrograde intussusception may occur in any portion of the gastrointestinal tract. A classification along anatomic lines is suggested.

(3) The diagnosis is difficult in most cases and will be made only at the time of operation.

(4) Early surgical interference is imperative.

REFERENCES

- ¹ Adams, A. W. Retrograde Jejuno-gastric Intussusception, Acute and Chronic. *Brit Med Jour*, 1, 248, 1935.
- ² Alvarez, W. C. The Mechanics of the Digestive Tract. New York, Paul B. Hoeber, Inc., 114, 1928.
- ³ Balfour, D. C. Primary Retrograde Intussusception of the Sigmoid Associated with Tumor. *ANNALS OF SURGERY*, 68, 588, December, 1918.
- ⁴ Becker, B. J. P. Retrograde Intussusception of the Jejunum Following Gastro-Enterostomy. *South African Med Jour*, 10, 489, June 11, 1936.
- ⁵ Bettman, R. B., and Baldwin, R. S. Retrograde Intussusception of Jejunum. A Complication of Gastro-Enterostomy. *J A M A*, 100, 1228, 1933.
- ⁶ Buckley, J. B. Superimposition of a Retrograde upon a Direct Intussusception. *Brit Med Jour*, 2, 665, 1919.
- ⁷ Caminiti, R. Occlusione intestinale retrograda ricorrente da diverticolo di Meckel invaginato ed invertito. *Policlinico (Sez. Chir.)*, 42, 261-273, May, 1935.
- ⁸ Croffi, A. Invaginazione retrograda ileale alta da tumore in un fanciullo. *Riforma Med*, 50, 612-617, April 21, 1934.
- ⁹ Clubbe, P. B. The Diagnosis and Treatment of Intussusception. London, Henry Frowde, 66, 1921.
- ¹⁰ Debenham, R. K. Retrograde Intussusception of the Jejunum Following Gastro-Jejunostomy. *Brit Med Jour*, 1, 250, 1935.
- ¹¹ Fitzwilliams, D. C. L. The Pathology and Etiology of Intussusception from the Study of 1,000 Cases. *Lancet*, 1, 628, 1908.
- ¹² Flemming, C. Retrograde Intussusception. *Lancet*, 2, 1136, November 13, 1937.
- ¹³ Goodear, Emil S. Retrograde Intussusception of Cecum into Ileum. *New York State Jour Med*, 38, 1397, November 1, 1938.

- ¹⁴ Langstaff, G Intussusception Edinburgh Med and Surg Jour , 3, 262, 1807
- ¹⁵ Lewis, E E A Case of Retrograde Intussusception Occurring During Life Brit Jour Surg , 23, 683, January, 1936
- ¹⁶ Perrin, W S , and Lindsay, E C Intussusception Brit Jour Surg , 9, 46, July, 1921
- ¹⁷ Power, D'Arcy Two Unusual Cases of Intussusception Trans Path Soc , 1, 121 1899
- ¹⁸ Power, D'Arcy A Case of Multiple Intussusception Trans Path Soc London, 37, 240, 1866
- ¹⁹ Romans, W H C , and Mitchiner, P H The Science and Practice of Surgery Philadelphia, Lea and Febiger, 663, 1933
- ²⁰ Schoenfeld, H H Retrograde Intussusception Virginia Med Monthly, 58, 242, July, 1931
- ²¹ Todyo, T Acute Intestinal Obstruction ANNALS OF SURGERY, March, 1938

DIVERTICULITIS OF THE COLON WITH SPECIAL REFERENCE TO THE SURGICAL COMPLICATIONS

ERNEST E. ARNHEIM, M.D.

NEW YORK, N. Y.

FROM THE SURGICAL SERVICES OF THE MOUNT SINAI HOSPITAL, NEW YORK, N. Y.

DIVERTICULA of the colon produce clinical manifestations when secondary pathologic changes of an inflammatory nature occur. These inflammatory changes may result in a variety of complications which call for surgical management. That surgical intervention in the treatment of diverticulitis of the colon is not infrequent is shown by a recent report by Brown and Marckley,² in which it is stated that, in the period from 1919 to 1929 in the Mayo Clinic, 277 cases of diverticulitis of the colon were treated medically, and 99 cases (26 per cent) were subjected to operation for this condition before or after coming to the Clinic.

The complications of diverticulitis of the colon requiring surgery may be listed as follows:

(1) Peritonitis resulting from passage of organisms through inflamed diverticula without perforation.

(2) Perforation of inflamed diverticula. In the more acute perforations varying degrees of peritonitis are present, but usually by the time perforation has occurred, protective adhesions have formed limiting the suppurative process and resulting in abscess formation.

(3) Fistula formation. Fistulae between the colon and the abdominal wall, the colon and the bladder, or the colon and another portion of the intestine may form by direct attachment and extension by necrosis, or by the secondary penetration of an abscess. There may be many submucous fistulae in the wall of the bowel.

(4) Peridiverticulitis. A chronic proliferative inflammation of the colon may occur as the result of repeated acute attacks. This chronic inflammation of the extramucosal part of the bowel wall results in a thickening of the colon with tumor-like formation, and narrowing of the lumen of the intestine. These cases may be confused with carcinoma of the colon because of the similarity in symptoms, and physical and roentgenologic findings.

(5) Metastatic suppuration.

(6) Carcinoma arising from diverticula of the colon.

Peritonitis Without Perforation of Diverticula—One would expect a peritonitis resulting from a passage of organisms through inflamed diverticula not infrequently as it occurs in acute appendicitis, since not only is the wall of an inflamed diverticulum damaged, but it is also quite thin. However, a review of the literature gives only a few, isolated case reports. The first of these was that by Loomis,¹⁹ in 1870, who found such a condition

at postmortem examination Other cases were reported by Cameron and Rippman,⁴ in 1910

Peritonitis and Abscess Secondary to Diverticulitis of the Colon with Perforation—The first case of diverticulitis of the sigmoid with perforation and diffuse peritonitis was described by Fiedler,⁹ in 1868, the condition being found at autopsy Jaboulay,¹² in 1897, was the first to operate upon a patient with diverticulitis of the sigmoid with diffuse peritonitis In 1911, Patel²⁶ collected from the literature 28 cases of diverticulitis of the sigmoid with perforation and peritonitis Some of these patients were operated upon and some were not, but the condition was fatal in all

Brewer,¹ in 1907, was the first in the American literature to report cases of diverticulitis of the sigmoid with perforation and abscess He cited six patients who were operated upon for this condition In the same year, Mayo, Wilson and Giffin²⁰ reported three cases of diverticulitis of the sigmoid with abscess

Telling,²⁹ in 1908, reviewed the literature and found 50 cases of diverticulitis of the sigmoid with perforation In 24 patients, this resulted in abscess, in 14, in diffuse peritonitis, and in one, in a perforation into a hernial sac In 1912, McGrath²¹ stated that there were 27 patients with diverticulitis of the colon operated upon in the Mayo Clinic from 1902 to 1912 Perforation occurred in six cases, resulting in abscess formation in four of them

Telling and Gruner,³⁰ in 1917, wrote a comprehensive article on diverticulitis of the colon, reviewing 324 cases in the literature In this series, abscess occurred in 28 per cent (90 cases), and diffuse peritonitis in 18 per cent (58 cases) Judd and Pollock,¹⁴ in 1924, reported on the experience of the Mayo Clinic from 1907 to 1924 There had been 118 cases of diverticulitis of the sigmoid in which operations were performed In this group, there were 17 cases of abscess, and one case of local peritonitis There were no instances of diffuse peritonitis

Fifield,¹⁰ in 1927, reviewed 52 cases of diverticulitis of the colon Perforation occurred in 24 patients, resulting in abscess in 11 instances, and diffuse peritonitis in nine In 1928, Monsarrot²² reported on 18 cases of diverticulitis of the colon Perforation was noted in ten patients, resulting in abscess in six instances, local peritonitis in two, and diffuse peritonitis in two In 1929, Newton²³ reviewed 44 cases of diverticulitis of the colon Perforation occurred in 13 patients, resulting in abscess in seven, local peritonitis in one, and diffuse peritonitis in three

Conway and Hitzrot,⁷ in 1931, reported on a series of 36 cases of diverticulitis of the colon There were 14 instances of abscess, and nine cases of varying degrees of peritonitis In the same year, Eggers⁷ reviewed 24 cases of diverticulitis of the colon Perforation occurred in seven patients, resulting in abscess in three of them, and diffuse peritonitis in four In 1934, Edwards⁶ reviewed 130 cases of diverticulitis of the colon Perforation with peritonitis occurred in four instances, abscess in three, and abscess with secondary perforation into the peritoneum in three Brown and Marcley,²

in 1937, reported on 88 cases of diverticulitis of the colon operated upon in the Mayo Clinic from 1919 to 1929. Perforation occurred in 17 patients, resulting in abscess in 11 instances, and varying degrees of peritonitis in six cases.

Thus, there is a great variation in the reported incidence of abscess and peritonitis resulting from diverticulitis of the colon with perforation, in the abscess group, varying from 4 to 39 per cent, and in the peritonitis group, varying from 0.8 to 25 per cent. In the entire group of 834 cases of diverticulitis of the colon, the incidence of abscess was 19 per cent, and peritonitis 12 per cent.

Fistulae—Jones,¹³ in 1859, reported the first case of diverticulitis of the sigmoid with a fistulous communication between the bladder and the sigmoid. This was an autopsy finding. In 1907, Mayo, Wilson and Giffin²⁰ reported three cases of diverticulitis of the sigmoid which resulted in fistulae between the sigmoid and bladder. In the 50 cases of diverticulitis of the sigmoid with perforation reviewed by Telling,²⁰ in 1908, 11 patients had vesico-intestinal fistulae.

Parham and Hume,²⁵ in 1909, reviewed 385 cases of vesico-intestinal fistulae, and reported that in 65 instances the cause was inflammatory. Although only three cases of diverticulitis of the colon were noted, it is likely that this condition was also present in others of the inflammatory group, especially as in many of these the fistulae were between the bladder and the sigmoid. In the group of 27 cases of diverticulitis of the sigmoid reported by McGiath,²¹ in 1912, there were fistulous communications with the bladder in two patients.

Bryan,³ in 1916, reviewed the literature of sigmoidovesical fistulae and found that 22 of the 42 cases were secondary to diverticulitis of the sigmoid. In Telling and Gruneir's³⁰ review of 324 cases of diverticulitis of the colon, in 1917, there were 38 instances of perforation into the bladder.

Sutton,²⁸ in 1921, reviewed 34 cases of vesicosigmoidal fistulae, and found diverticulitis of the colon present in six instances. In the group of 118 cases of diverticulitis of the sigmoid reported by Judd and Pollock,¹⁴ in 1924, there were eight instances of fistulae between the sigmoid and the bladder.

Fifield,¹⁰ in 1927, reported four cases of vesicocolic fistulae in a group of 52 cases of diverticulitis of the colon. In 1929, Newton²³ noted two cases of sigmoidovesical fistulae in a group of 44 cases of diverticulitis of the colon. Rankin and Brown,²⁷ in 1930, reported 48 operated cases of sigmoidovesical fistulae in a group of 481 cases of diverticulitis of the colon.

In 1932, Lett¹⁷ reported seven instances of vesicosigmoidal fistulae in a group of 172 cases of diverticulitis of the colon. Lockhart-Mummery,¹⁸ in discussion, observed four cases of sigmoidovesical fistulae in a group of 87 cases of diverticulitis of the colon. Nitch,²⁴ in discussion, stated that in 20 cases of diverticulitis of the colon, seven cases developed vesicocolic fistulae.

In a group of 130 cases of diverticulitis of the colon reviewed by Edwards,⁶ in 1934, there were two instances of fistulae between the sigmoid

and bladder. Brown and Marcle,² in 1937, reported 15 cases of sigmoidovesical fistulae in a group of 88 cases of diverticulitis of the colon. Kellogg,¹⁵ in 1938, reviewed 88 cases of vesico-intestinal fistulae, and reported 37 instances of diverticulitis of the colon.

Thus, fistulae between the sigmoid and the bladder are relatively frequent complications of diverticulitis of the sigmoid, and such complications are more common in this condition than in carcinoma of the sigmoid. There is a wide variation in the reported incidence of sigmoidovesical fistulae resulting from diverticulitis of the colon, varying from 15 to 35 per cent, but in the entire group of 1,516 cases of diverticulitis of the colon the incidence was 8 per cent.

Peridiverticulitis —In 1907, Mayo, Wilson and Giffin²⁰ reported five cases in which a portion of the sigmoid was excised for diverticulitis of the sigmoid with tumor-like formation and obstruction (peridiverticulitis). These were the first recorded instances in which the pathologic changes in diverticulitis of the colon were demonstrated during life. McGlath,²¹ in 1912, reported the pathologic changes of peridiverticulitis in 26 of the 27 cases of diverticulitis of the colon operated upon at the Mayo Clinic from 1902 to 1912.

Telling and Gunner,³⁰ in 1917, noted an incidence of 24 per cent (78 cases) of peridiverticulitis in their review of 324 cases of diverticulitis of the colon. In 1927, Fifield¹⁰ reported evidences of intestinal obstruction due to peridiverticulitis in 30 per cent (16 cases) of 52 cases of diverticulitis of the colon. Newton,²³ in 1929, reported two cases of large intestinal obstruction in 44 cases of diverticulitis of the colon.

In 1930, Rankin and Brown²⁷ reported an incidence of 31 per cent (71 cases) of tumefaction in 481 cases of diverticulitis of the colon. Conway and Hitziot,⁵ in 1931, noted two cases of stenosis of the colon in a group of 36 cases of diverticulitis of the colon. Eggers,⁷ in the same year, reported nine cases with obstruction of the colon, due to a mass, in 24 cases of diverticulitis of the colon. Brown and Marcle,² in 1937, reported on 88 cases of diverticulitis of the colon operated upon at the Mayo Clinic from 1919 to 1929. In this group, 41 cases were subjected to colon resections because of the evidence of peridiverticulitis.

In the reported incidence of peridiverticulitis in cases of diverticulitis of the colon, there is a wide variation of different reports, from 6 to 96 per cent. In the entire group of 1,049 cases of diverticulitis of the colon, the incidence of peridiverticulitis was 20 per cent.

Metastatic Suppuration —There are three reported cases of diverticulitis of the colon with metastatic suppuration, the evidences of which being found at autopsy. The first case was reported by Whyte,¹ in 1906. His patient died of multiple liver abscesses. In 1921, Foggie¹¹ reported a case of diverticulitis of the colon with multiple lung abscesses and a brain abscess. Kramer and Robinson,¹⁶ in 1926, reported the first case of diverticulitis of the colon with pylephlebitis. This patient had a suppurative phlebitis of the mesenteric,

splenic and portal veins, a suppurative hepatitis and cholangitis, and multiple liver abscesses

Carcinoma—Diverticulitis of the colon bears no etiologic relationship to carcinoma of that organ. Occasionally the two conditions may coexist, but such an occurrence is incidental. This was demonstrated by Rankin and Brown,²⁷ in 1930, who reported that in 227 cases of diverticulitis requiring operation, coexisting carcinoma was found in only four instances. The same authors noted that diverticulosis of the colon was found in only four instances in a group of 679 operated cases of carcinoma of the colon. Fallon,⁸ in 1930, reported 625 cases of diverticulitis of the colon in 1,800 cases of diverticulosis of the colon. Coexisting carcinoma was found in 0.5 per cent of the cases. Diverticulitis of the colon was associated with carcinoma in 19 cases in a group of 1,600 operated cases of carcinoma of the colon.

SUMMARY OF A REVIEW OF THE LITERATURE—Diverticulitis of the colon progressed to the development of surgical complications in over one-half of the cases, in the following incidence: Peridiverticulitis 20 per cent, abscess 19 per cent, peritonitis 12 per cent, and sigmoidovesical fistula 8 per cent.

In the ten-year period, 1927–1937, there was 35 cases of diverticulitis of the colon admitted to the Surgical Services of the Mount Sinai Hospital. There were no surgical complications in 16 of these cases. The type and incidence of surgical complications in the remaining 19 cases were as follows: Peritonitis without perforation in two, abscess in five, perforative peritonitis in five, stenosis (peridiverticulitis) in four, sigmoidovesical fistula in two, and associated carcinoma in one.

The essential features of the cases of diverticulitis of the colon without surgical complications are summarized in Table I.

The following are the case records of the 19 cases of diverticulitis of the colon with surgical complications.

PERITONITIS WITHOUT PERFORATION

Case 1—Hosp. No. 267893. S. K., female, age 59, was admitted to the hospital, May 31, 1927, with the complaint of severe, lower abdominal pain of 12 hours' duration. There had been previous attacks of lower abdominal pain and marked constipation for 20 years. Temperature 102.4° F. There was tenderness and spasticity in both lower quadrants of the abdomen, more marked on the right side. Leukocytes 20,000, 90 per cent polymorphonuclears.

A preoperative diagnosis of acute appendicitis with local peritonitis was made, and a celiotomy was performed on the day of admission. Thin, brown, odorless fluid was found in the pelvis. There was fibrinous exudate on the wall of the sigmoid at the site of the inflamed diverticula. The appendix was removed and the pelvis drained at site of the inflamed diverticula of the sigmoid. The convalescence was uneventful, and the patient was discharged 35 days after operation.

Case 2—Hosp. No. 276653. R. B., male, age 39, was admitted to the hospital, August 10, 1927, with a history of generalized abdominal pain for eight days, fever and obstipation for seven days, and a chill on the day before admission. The patient was acutely ill. Temperature 106.2° F. The abdomen was distended, and there was generalized abdominal tenderness and spasticity.

DIVERTICULITIS OF THE COLON

TABLE I

DIVERTICULITIS OF THE COLON WITHOUT SURGICAL COMPLICATIONS

Case	Age	Sex	History	Physical Examination	Laboratory Data	X-Ray	Course
1	66	F	Constipation for many years, bloody diarrhea for 1 day	Temperature 100.6° F, obesity	Hemoglobin 53%, W B C 8 400 polys 64%, gross blood in stools	Multiple large diverticula and marked spasticity of entire colon	Improved, recurrence of bloody stools 2 yrs later, died 4 yrs later—cause unknown
2	83	F	Upper abdominal pain for 2 wks, constipation for 10 days	Temperature 101° F, obesity	W B C 8 200 polys 73%	2 diverticula and marked spasticity of sigmoid	Improved
3	66	F	Constipation for 10 yrs, epigastric pain for 3 yrs, loss of weight for 8 mos	Temperature 100.4° F	W B C 5 600 polys 50%	Many diverticula in descending colon and sigmoid with marked spasticity of sigmoid	Improved, symptom-free 6 mos later
4	72	F	Upper abdominal pain, nausea, vomiting and abdominal distention for 2 yrs, marked upper abdominal pain and constipation for 3 days	Temperature 102° F, generalized abdominal tenderness and distention, obesity	W B C 23 900 polys 91%	Several large diverticula and marked spasticity of sigmoid	Improved, occasional abdominal pain 3 yrs later
5	67	M	Lower abdominal pain and constipation for 5 days	Temperature 99.6° F, mass in left lower quadrant of abdomen	W B C 14 000 polys 87%	Many diverticula and spasm of sigmoid	Improved, died 3 yrs later—cause unknown
6	68	M	Lower abdominal pain and constipation 10 yrs ago and for past 8 days	Temperature 101.6° F, tenderness in lower left quadrant of abdomen	W B C 16 000 polys 81%	Several small diverticula and spasm of sigmoid	Improved
7	57	F	Constipation for many years, abdominal pain for 3 days	Temperature 100.4° F, tenderness in left lower quadrant of abdomen	Guaiac positive stool	Several small diverticula of sigmoid	Improved
8	76	F	Diarrhea for 13 yrs, abdominal pain for 2 yrs	Temperature 100° F, obesity	W B C 9 100 polys 78%	Diverticula of sigmoid with marked spasm of descending colon and sigmoid	Improved, symptom-free 1 yr later
9	66	F	Generalized abdominal pain and diarrhea for 3 wks	Temperature 100.2° F, sigmoidoscopy negative	W B C 6 300 polys 58%	Diverticula of ascending and descending colon and sigmoid with moderate spasm of sigmoid	Improved
10	64	M	Constipation 1 mo	Temperature 103° F, sigmoidoscopy negative	W B C 30 800 polys 82% guaiac positive stool	Many diverticula and spasm of descending colon	Improved

TABLE I (Continued)

Case	Age	Sex	History	Physical Examination	Laboratory Data	X-Ray	Course
11	76	F	Diarrhea and loss of weight for 8 mos	Temperature 100.6° F, spasm at rectosigmoid on sigmoidoscopy	Guaiac positive stool	Diverticula and spasm of sigmoid	Improved, recurrence of diarrhea 4 yrs later
12	77	M	Constipation for many years generalized abdominal pain and loss of weight for 3 mos	Temperature 99.2° F, sigmoidoscopy negative	Guaiac positive stool	Diverticula of hepatic flexure descending colon and sigmoid with marked spasm of descending colon and sigmoid	Improved
13	78	M	Abdominal pain and constipation for 3 days	Temperature 104° F, tenderness in right upper quadrant of abdomen abdominal distention	W B C 8 000 polys 80%	Many diverticula and spasm of descending colon and sigmoid	Improved
14	70	F	Diarrhea and vomiting 6 and 3 yrs ago diarrhea upper abdominal pain and loss of weight for 3 mos	Temperature 100.2° F marked spasm and injection of mucosa of sigmoid on sigmoidoscopy	W B C 6 200 polys 72%	Many small diverticula and spasm of sigmoid, diverticulum of second part of duodenum	Improved
15	64	F	Pain in left lower quadrant of abdomen and blood in stool for 2 days	Temperature 102° F tenderness in left lower quadrant of abdomen	W B C 19 000 polys 84%	Many small diverticula and spasm of sigmoid	Improved
16	50	F	Lower abdominal pain for 2 days	Temperature 100.4° F, tenderness and spasm in left lower quadrant of abdomen	W B C 11 300 polys 60%	Diverticula of descending colon and sigmoid with spasm of sigmoid	Improved

A preoperative diagnosis of acute appendicitis with diffuse peritonitis was made, and a celiotomy was performed on the day of admission. A diffuse peritonitis was found, and an appendectomy and drainage was performed. The patient died five hours after admission. The culture of the peritoneal fluid was reported *Streptococcus haemolyticus*.

Autopsy—The peritoneum was dull and covered by fibrinous exudate, with about 200 cc of sanguinopurulent fluid in the peritoneal cavity. The peritonitis was most marked in the pelvis. Some coils of lower ileum were lightly adherent to the sigmoid. The sigmoid was found to be markedly indurated and adherent to the posterior peritoneum. The regional lymph nodes of the sigmoid were enlarged. When opened, the colon showed numerous inflamed, narrow-mouthed diverticula extending from the ascending colon to the sigmoid.

PERFORATION WITH ABSCESS

Case 3—Hosp No 265596 R M, male, age 38 was admitted to the hospital, March 29, 1927, with the complaint of pain in the left lower quadrant of the abdomen and left

flank of three days' duration. Temperature 102.6° F. There was tenderness in the epigastrium, and tenderness and spasticity in the left upper quadrant of the abdomen. Leukocytes 18,000, 86 per cent polymorphonuclears.

During the first week of hospitalization, the patient ran a temperature from 101° to 103.8° F. The abdominal signs and leukocytosis continued. Clinical and roentgenologic evidences of a consolidation of the lower left lobe developed. Tenderness over the left lower ribs was noted. The patient was thought to have a left subphrenic abscess, and he was operated upon one week after admission. A large abscess under the left diaphragm, mesial and lateral to the spleen, was incised and drained.

Postoperative Course—The patient ran a stormy course. Elevated temperature continued for about two months. A fecal discharge was noted from the wound soon after operation and persisted for five weeks. There were persistent clinical and roentgenologic signs of a pneumonia of the left lower lobe. A barium enema, two months after operation, revealed a large diverticulum in the upper portion of the descending colon with considerable spasm of the entire descending colon. The tip of a drainage tube was close to the site of the diverticulum. The patient was discharged two months after admission.

Subsequent Course—The patient was readmitted four years later, with a history of lower abdominal pain and fever of three days' duration. Temperature 104° F. There was tenderness and spasticity in the left lower quadrant of the abdomen. Leukocytes 18,200, 82 per cent polymorphonuclears.

The temperature dropped steadily, and was normal by the fourth day of hospitalization. By this time, the abdominal signs had disappeared, and the leukocytes were normal. During the second week of hospitalization a mass was felt in the left lower quadrant of the abdomen. The patient was discharged three weeks after admission.

The patient remained well for a period of four years, when he was again readmitted because of pain in the epigastrium and upper right quadrant of two days' duration. There was tenderness in right upper quadrant, and a roentgenogram of the gallbladder showed failure of visualization. A cholecystectomy for chronic cholecystitis and cholelithiasis was performed. The patient's convalescence was uneventful.

Case 4—Hosp. No. 295313. J. G., male, age 55, was admitted to the hospital, October 3, 1928, with the history of a chill ten days previously. This was followed on the next day by pain in the lower abdomen in the midline, and on the left side, which continued until admission. For five days the patient had had chills and had run a temperature up to 104° F. Thereafter the chills stopped, but the temperature continued.

On admission, the temperature was 102° F. There was marked tenderness in the left lower quadrant of the abdomen. On rectal examination there was a small, tender mass high up on the left side. Leukocytes 5,200, 68 per cent polymorphonuclears. Barium enema showed spasm of the sigmoid. The patient continued to have an elevated temperature up to 101.6° F. for two weeks.

Operation—Two weeks after admission. Spinal anesthesia. The sigmoid was bound down to the bladder anteriorly, the small intestine mesially, and the lateral pelvic wall laterally. On separating the sigmoid from the lateral pelvic wall, an abscess was encountered containing two ounces of thick, creamy, odorless pus. The sigmoid and its mesentery in this region felt indurated, and the operator was in doubt as to whether this induration was due to neoplasm or inflammation. On the anterior and lateral walls of the sigmoid there were multiple diverticula, and on the posterior wall a perforation could be seen which entered the mesentery. After the abscess was evacuated the mesosigmoid was ligated, and a Mikulicz exteriorization of the sigmoid was performed, draining the mesentery on either side with packing and rubber dam. A tube was placed in the pelvis. The culture of the pus was reported *B. coli*.

The exteriorized sigmoid was found to be necrotic, and was excised two days after operation. Clinical evidences of peritonitis developed and the patient died two weeks after operation.

Autopsy—There was a gangrenous inflammation of the abdominal wound and tissues surrounding the operative site with localized pelvic peritonitis. There were many inflamed diverticula of the sigmoid.

Case 5—Hosp No 345651 P K, male, age 57, was admitted to the hospital, November 14, 1932, with a history of right lower quadrant abdominal pain, constipation, and vomiting of four months' duration, loss of weight for two months, and a chill two weeks before admission, with continuous fever since then. Temperature 98.6° F. Examination of the abdomen showed slight tenderness in the right upper quadrant. Barium enema revealed spasm and many diverticula of the sigmoid. On the twelfth day of hospitalization the stools became grossly bloody. Two days later there was a rise in temperature to 103° F, associated with lower abdominal pain and bloody stools. Rectal examination revealed a mass on the left side extending upward. On sigmoidoscopy, there was found to be an obstruction at the rectosigmoid, with a polypoid appearance of the mucosa at that site.

Operation—Seventeen days after admission. Spinal anesthesia. The sigmoid was found to be rather short and fixed. Several diverticula of the sigmoid were seen. An abscess, posterior to the sigmoid, was entered and about two ounces of thick, creamy, odorless pus was evacuated. A rubber tube drain was inserted into the abscess cavity. The culture of the pus was reported *B. coli*.

The patient's postoperative course was uneventful except for some wound infection until the tenth day, when the temperature rose to 104° F, and he died 36 hours thereafter.

Autopsy—There was an inflammatory mass involving the sigmoid, omentum and a loop of ileum in which there were a number of small abscesses containing green pus. The descending and sigmoid colon was adherent to the lateral parietal peritoneum. The abscess to the left of the sigmoid had been drained. From the abscess cavity, a probe could be inserted through a small perforation into the lumen of the sigmoid at the site of a perforated, inflamed diverticulum. At the site of attachment of the ileum to the sigmoid, there was an ileosigmoidal fistula. The wall of the sigmoid was greatly indurated. The mucosa was thickened, reddened and granular. There were many diverticula of the sigmoid, the mouths of which were patent but narrow. Most of the diverticula contained fecoliths.

Case 6—Hosp No 406338 C R, female, age 38, was admitted to the hospital, March 27, 1937, with the history of chills and fever starting 16 days before admission. The following day she began to complain of left lower quadrant abdominal pain which persisted until admission. Associated with the onset of the abdominal pain, there was severe, nonbloody diarrhea which lasted for three days. The patient vomited several times during the first two days of her illness. The chills and fever subsided after the first day of the illness, but recurred daily for three days prior to admission. Temperature 103.2° F. Examination revealed a large, hard, tender mass in both lower quadrants of the abdomen, more on the left side, extending to the umbilicus. There was tenderness and spasticity in both lower quadrants of the abdomen away from the mass, more on the left side. Pelvic examination revealed a hard, nodular mass in the pelvis. Leukocytes 18,700, 80 per cent polymorphonuclears. The temperature continued to be elevated, the mass became larger, and the patient's general condition became worse. On the third day of hospitalization, the temperature rose to 105.2° F.

Operation—Three days after admission. Avertin-gas-oxygen-ether anesthesia. There was some clear, yellow fluid in the peritoneal cavity, with dilatation of the small intestine. A large, hard mass occupied almost all of the left lower quadrant. The sigmoid was separated from the lateral pelvic wall, and an abscess was entered containing about two ounces of thick, foul-smelling, green pus and air. The abscess was drained by tube and packings. The patient's condition remained poor and she died during the first postoperative day.

Autopsy—In the pelvis, especially on the left side, there were an adherent series of ileal loops to a large mass, the size of a grapefruit. The rubber tube drain and packings entered a bilocular abscess cavity, each locule measuring about 7½ cm in diameter. The walls of the cavities were lined by a thick, rough, shaggy, green exudate, and in one locule there was about 200 cc of turbid, thin, green, foul-smelling fluid. The other locule was empty. The abscess cavity was bounded by the bladder anteriorly, the uterus mesially, the left broad ligament and the sigmoid posteriorly, and the pelvic peritoneum and sigmoid laterally. An undrained abscess cavity was found posteriorly behind the left broad ligament, between it and a pedunculated fibroid arising from the posterior wall of the uterus. The cavity was about 6¼ cm in diameter, was not connected with the anterior drained abscess, and contained about 100 cc of thin, green, foul-smelling fluid. The wall of the sigmoid was thickened. The serosal surface formed a part of the lateral wall of the large, anterior abscess. Three diverticula were found in the sigmoid. Two of these were perforated, entering the anterior and posterior abscesses, and the third was intact.

Case 7—Hosp No 415178 F C, male, age 35, was admitted to the hospital, October 9, 1937, with the complaint of lower abdominal pain of eight days' duration. The pain had gradually decreased in severity until the day before admission, when it became severe following an enema. During the same period he had nausea and an intermittent temperature up to 102° F. He had always been constipated. Temperature 102.8° F. On rectal examination a tender exudate was felt high up. Leukocytes 22,100, 89 per cent polymorphonuclears.

The patient was given intravenous fluids for a week, and during this period a Levin tube was used to combat abdominal distention. During this time, the temperature ranged from 99.4° to 103.4° F. The leukocytes dropped to 13,700, with 80 per cent polymorphonuclears. At the end of the first week of hospitalization, the rectal exudate was less, the tenderness decreased, and the spasticity had disappeared. During the second week of observation, the rectal mass became smaller, and an indefinite mass was felt in the lower abdomen. The temperature ranged between 99.2° and 102° F, leukocytes 12,400, with 80 per cent polymorphonuclears. During the third week, the rectal mass could not be felt, and the abdominal mass was still questionable. The temperature varied between 99° and 101.8° F, leukocytes 11,900, with 83 per cent polymorphonuclears. During the fourth week, the mass in the lower abdomen was distinctly palpable.

Operation—Five weeks after admission. Avertin-gas-oxygen-ether anesthesia. A pelvic abscess was found which contained about six ounces of thick, green, odorless pus. The appendix was not acutely inflamed. The abscess was drained with Penrose drains. The culture of the pus was reported *B. alkaligenes*. A fecal fistula was noted one week postoperative, which lasted for two weeks. A low grade fever continued until discharge. The patient left the hospital three weeks after operation.

Subsequent Course—A barium enema performed three months after discharge revealed diverticula and spasm of the sigmoid. The patient was symptom-free for a period of 16 months, when he was readmitted with the complaint of lower abdominal pain of four days' duration. The examination was negative except for a ventral hernia at the operative site. Sigmoidoscopy was negative, and the barium enema revealed the diverticula and spasm of the sigmoid. The abdominal pain soon subsided and the patient was discharged in ten days.

PERFORATION AND PERITONITIS

Case 8—Hosp No 277092 Baby S, male, age 18 hours, was admitted to the hospital, February 25, 1927, with abdominal distention, obstipation and vomiting since birth. The child was full term, and there was nothing unusual about the delivery. Temperature 100° F, and the abdomen was markedly distended.

Operation—Two hours after admission. Ether anesthesia. The peritoneal cavity was filled with dark brown fluid. The small intestines were distended, purple in color,

and covered by fibrinous exudate. An ileostomy was performed. Following operation, the child's condition remained poor, and he died three days after operation.

Autopsy—The peritoneal cavity contained about 50 cc of brown fluid. The peritoneum and peritoneal surfaces of the abdominal organs were coated with a fibrinous exudate which assumed a plastic character in the upper abdomen, especially over the liver, omentum and spleen. The enterostomy tube was found in the ileum, about 15 cm above the ileocecal valve. The small intestine proximal to this was moderately distended. The remainder of the ileum and the large intestine were collapsed. The omentum was rolled up and lay in the left upper quadrant. It was greenish-black in color, and in attempting to separate it from the surrounding adherent structures, it was found to enclose a large abscess cavity. There was an inflamed, perforated diverticulum of the splenic flexure of the colon, which opened into the abscess cavity.

Case 9—Hosp No 288489 M R, female, age 71, was admitted to the hospital, February 25, 1928, with the history of generalized abdominal pain and obstipation for two days, and vomiting for one day. Temperature 103° F. The abdomen was distended, and there was generalized abdominal tenderness and spasticity. Leukocytes 8,600, 96 per cent polymorphonuclears. Soon after admission, the pulse became very irregular, and there was marked circulatory collapse. The patient's poor condition continued, and she died one week after admission.

Autopsy—The peritoneal cavity contained about 300 cc of yellow pus and fibrin. There was a large diverticulum, about 2 cm in diameter, in the duodenum just below the papilla of Vater. In the cecum there were three small diverticula. There were several small diverticula of the sigmoid, one of which had perforated. The sigmoid wall was necrotic around the perforated area.

Case 10—Hosp No 348476 E M, female, age 44, was admitted to the hospital, January 29, 1933, with the history of lower abdominal pain following the taking of Epsom salts, vomiting and diarrhea of three days' duration, and a chill one hour before admission. Temperature 104.4° F. There was a diffuse abdominal tenderness and spasticity, most marked in the left lower quadrant. In the latter region, a large indefinite mass could be felt.

Operation—Four hours after admission. Spinal anesthesia. The peritoneal cavity contained free, turbid fluid. Loops of bowel and omentum were adherent in the region of the sigmoid, forming a large mass which extended down into the pelvis. The small intestine was congested, dilated, and covered with flakes of fibrin. Thick pus was found in the pelvis. Two small necrotic areas were found on the anterior wall of the sigmoid. This loop of the sigmoid was exteriorized, and the abdomen was drained. The patient's condition remained poor, and she died during the first postoperative day.

Autopsy—The exteriorized loop of sigmoid was dark red in color and presented an opening about 4 mm in diameter into its lumen. There was seropurulent fluid in the pelvis, in both lumbar gutters, and under the liver. Several collections of thick, green pus were found between intestinal loops. The intestines were markedly dilated. The descending colon and sigmoid showed many diverticula, two of which in the sigmoid had perforated.

Case 11—Hosp No 375348 R S, male, age 28, was admitted to the hospital, January 5, 1935, with the complaints of para-umbilical pain and nausea of 14 hours' duration. He vomited and had a chill one hour after onset of the pain. He had had two previous attacks of abdominal pain, one seven months and the other six weeks before. Temperature 103.4° F. There was marked tenderness and spasticity in both lower quadrants of the abdomen. On rectal examination, there was tenderness and fullness high up. The preoperative diagnosis was acute appendicitis with local peritonitis.

Operation—Three hours after admission. Gas-oxygen-ether anesthesia. The peritoneal cavity contained a large amount of thin, greenish-yellow fluid. The appendix was not acutely inflamed. The loops of small intestine in the pelvis were reddened. There was a small amount of fibrin on the sigmoid. A small, necrotic area with an

obvious perforation was found in the wall of the sigmoid near the mesenteric attachment. Two fatty beads presented close to the area of perforation. The perforation was closed, and drainage instituted to the site of perforation.

The culture of the pus was reported *B. coli*. The postoperative course was uneventful. Intravenous fluids were given for three days. The temperature was normal by the fifth postoperative day. The patient was discharged on the fifteenth postoperative day.

Case 12—Hosp. No. 389034. S. H., male, age 49, was admitted to the hospital, January 20, 1936, with the history of lower abdominal pain, constipation, vomiting and fever of six days' duration. Temperature 99.2° F. There was generalized abdominal tenderness and spasticity. On rectal examination a firm, tender mass was felt on the left side. Leukocytes 8,600, 69 per cent polymorphonuclears. The temperature rose to 103.6° F. 16 hours after admission. The leukocytes were 20,800, 90 per cent polymorphonuclears, on the second day of hospitalization. The patient's condition steadily grew worse, the temperature ranging between 103° and 105° F. His condition was felt to be too poor for surgical intervention. The patient died on the fifth day of hospitalization.

Autopsy—The peritoneal cavity contained about 500 cc. of thick, gray, purulent fluid, much of which was accumulated in many locules between loops of intestine. There were large collections of purulent fluid beneath the liver, in the right lower quadrant and in the pelvis. The loops of small intestine were distended, discolored and adherent to each other. The omentum was adherent to the sigmoid. The colon was moderately dilated. The sigmoid and the distal third of the transverse colon presented about ten diverticula, some of which were filled with inspissated fecal material. There was one large diverticulum about 1 cm. in diameter, in the posterior wall of the sigmoid, 5 cm. proximal to the rectosigmoid. This opened into a cavity 3 cm. in diameter, the walls of which were formed by the sigmoid and retroperitoneal tissues. From here, a tract ran posteriorly and mesially into the peritoneal cavity. The serosa of the sigmoid and the proximal 10 cm. of rectum were thickened.

PERIDIVERTICULITIS

Case 13—Hosp. No. 256430. M. C., male, age 48, was admitted to the hospital, January 25, 1927, with the history of constipation, and difficulty in starting the urinary stream of two weeks' duration. Physical examination was negative except for a mass felt on rectal examination. Sigmoidoscopy and barium enema revealed an obstruction in the sigmoid.

Operation—The sigmoid was found to be bound down in the pelvis by dense adhesions. About two inches of the sigmoid were involved in a dense, hard mass, feeling like carcinoma. This region of the sigmoid was excised, and a side-to-side anastomosis was performed. Examination of the specimen showed a thickened wall of the sigmoid, with the mouths of several diverticula seen in the mucosa. There was no evidence of malignancy. The patient's convalescence was complicated by multiple neuritis. The patient was discharged well six weeks after operation.

Case 14—Hosp. No. 285674. I. K., male, age 73, was admitted to the hospital, November 25, 1927, with the history of obstipation and abdominal distention for two weeks, and generalized abdominal pain for five days. Temperature 101.4° F. There was marked abdominal distention, and some generalized abdominal tenderness and spasticity. The patient refused operation, and died the next day from circulatory failure.

Autopsy—There was a marked distention of the colon. The sigmoid was collapsed and adherent to the posterior parietal peritoneum. A firm tumor mass was felt in this region of the sigmoid. The visceral peritoneum was reddened, and the peritoneal cavity contained about 300 cc. of brownish, cloudy fluid. There were many small diverticula filled with fecal material in the descending colon. The sigmoid was markedly stenosed. There were many diverticula in the sigmoid which penetrated the muscular layer and

extended into the underlying fat tissue. The muscular layer of the sigmoid was very hypertrophied. There were several small ulcerations in the dilated cecum.

Case 15—Hosp No 315672 J L, male, age 54, was admitted to the hospital, June 21, 1930, with the history of a painful swelling in the left lower quadrant of the abdomen and diarrhea of six months' duration. Temperature 99.4° F. There was an elastic, tender, egg-sized mass in the left lower quadrant of the abdomen. The stool was guaiac positive and purulent. Leukocytes 8,800, 84 per cent polymorphonuclears. Sigmoidoscopy showed an obstructing mass at the rectosigmoid, covered by inflamed mucosa and a purulent membrane. A biopsy from the region was reported chronic and acute inflammation. A barium enema showed a marked spasticity of the sigmoid. There were many diverticula of the colon extending from the cecum to the sigmoid. One of the diverticula, at the junction of the descending colon and sigmoid, extended about one-half inch extralumenally.

Operation was advised, but the patient refused and left the hospital. He died five years later. The cause of death was not known.

Case 16—Hosp No 321003 J C, male, age 65, was admitted to the hospital, December 6, 1930, with the history of frequency of urination and dysuria of one month's duration. Rectal examination revealed an enlargement of the prostate. Pus and red cells were found in the urine. Temperature 98.6° F. Leukocytes 8,600, 70 per cent polymorphonuclears. Cystoscopic examination disclosed an enlargement of the middle lobe of the prostate, and a suprapubic cystotomy was performed, in the course of which an extravesical mass was felt through the posterior wall of the bladder. Because of this finding, attention was directed to the colon. Sigmoidoscopy demonstrated an intussusception of the sigmoid into the rectum which made the examination unsatisfactory. A barium enema showed a marked delay to the passage of the barium at the distal portion of the sigmoid about eight inches from the anus. The barium progressed along a constricted position for distance of about one inch. With more pressure the obstruction was partially overcome.

Operation—Spinal anesthesia. A large mass in the region of the rectosigmoid was found. The mass was densely adherent to the bladder and between the two there was a small perisigmoidal abscess. The lesion was considered to be a carcinoma. The mass was excised, and an end-to-end anastomosis of the divided ends of the sigmoid was performed. The pathologic report was diverticulitis and perisigmoiditis. The patient died one week after operation. There was no autopsy, but there were clinical evidences of peritonitis.

SIGMOIDOVESICAL FISTULA

Case 17—Hosp No 334704 A R, male, age 39, was admitted to the hospital July 27, 1929, with a left inguinal hernia of seven months' duration, and diarrhea and hematuria of three months' duration. His Wassermann was four plus, and he was given antiluetic therapy. He was readmitted four months later, with the history of urinary frequency and dysuria, vomiting and chills of four months' duration. No cause was found for these symptoms. Four months later, the left inguinal hernia was repaired. He was readmitted two years later, with the history of bloody diarrhea, abdominal pain, weakness and loss of 20 pounds in weight of three months' duration. There was a firm, tender mass in the left lower quadrant of the abdomen. On sigmoidoscopy, the rectal mucosa was found to have a granular appearance. A biopsy of this tissue was reported granulation tissue with chronic inflammation. A barium enema showed a partial obstruction in the region of the midsigmoid. Some barium was able to pass this region into the descending colon which appeared dilated. There was considerable spasticity and many diverticula of the sigmoid. While under observation, the patient had recurrent attacks of abdominal pain, and in one of these the leukocytes were 25,000, 88 per cent polymorphonuclears. Under conservative therapy the patient's symptoms subsided.

DIVERTICULITIS OF THE COLON

The last admission was January 27, 1932, two months after the previous one. During this period he continued to have diarrhea and dysuria. There was a hard, slightly tender mass in the left lower quadrant of the abdomen. On sigmoidoscopy, the granular appearance of the rectal mucous membrane was again noted. The stool contained a mixture of mucus and blood. Leukocytes 8,800, 54 per cent polymorphonuclears. While under observation, the patient was noted to pass gas from the urethra during urination. On cystoscopy, an edematous, polypoid mass covered by exudate was found on the posterior wall of the bladder. A fistula in this region could not be demonstrated.

Operation—Spinal anesthesia. The lower sigmoid and rectosigmoid were found to be the site of an inflammatory mass which bound them to the posterior wall of the bladder. A sigmoidovesical fistula was demonstrated, and the openings in the sigmoid and bladder were closed. The sigmoid was markedly thickened and edematous. The diseased sigmoid, about 15 cm in length, was excised, and an end-to-end anastomosis of the cut ends of the sigmoid was performed, followed by a tube cecostomy. Examination of the specimen showed the wall of the sigmoid to be white, firm and cartilaginous in consistency, with some polyposis of the mucous membrane. Three diverticula were found. The pathologic report was chronic diverticulitis with fibrosis and perisigmoidal acute and chronic inflammation. The patient died five days after operation with clinical evidences of peritonitis.

Autopsy—The site of the end-to-end anastomosis of the sigmoid, except for a few sutures, was open posteriorly. The distal margin of the anastomosis and the lower 6 cm of the rectum were blackish-red in color and showed a number of shallow, irregular ulcerations. The intervening mucosa, although dark in color, was not necrotic. The bladder wall was thickened. Sutures were present in the posterior wall of the bladder. On the posterior aspect of the fundus a mouth of a sinus tract was found which led to the sutured area posteriorly. The small and large intestines were distended and adherent to each other by fibrinous exudate. There was a moderate amount of sero-purulent fluid in the peritoneal cavity.

Case 18—Hosp No 346502. M. S., male, age 59, was admitted to the hospital, December 7, 1932, with a history of frequency of urination and dysuria of six years' duration. For three weeks prior to admission, these symptoms had become more marked, the patient passing thick, bloody urine every hour. The patient's bowel movements were fluid in character, and for three weeks preceded each voiding. Temperature 101° F. On rectal examination, there was a large area of induration extending upward from the left lobe of the prostate. The patient was passing grossly purulent and bloody urine. Blood urea 34 mg per 100 cc. A roentgenogram of the urinary tract showed a large number of irregular concretions in the region of the symphysis pubis, which were interpreted as prostatic calculi.

In view of the grossly purulent urine, it was felt that any attempt to catheterize the patient would be followed by an epididymitis. Accordingly, a section of the vas deferens on both sides was performed. On the day following this procedure, the patient stated urine came through the rectum. On further questioning, he stated that he had passed urine from the rectum for a month prior to admission. A catheter was passed and methylene blue was injected into the bladder. The dye was seen in the rectum through a proctoscope. The exact site of vesicorectal communication could not be seen.

A suprapubic cystotomy was performed, 12 days after admission. The bladder contained thick, brown fluid and pieces of necrotic tissue. The prostate was enlarged and contained small calculi. The bladder was drained. Just prior to operation, the patient appeared quite ill. The abdomen was distended and the pulse 150. The clinical picture suggested a peritonitis. Following the suprapubic cystotomy his general condition improved, although the abdominal distention persisted. On sigmoidoscopy, an obstruction was met about 15 cm from the anus. In view of the persistent abdominal distention, a transverse colostomy was performed under local anesthesia. The ascending, transverse and descending colon were greatly dilated. Following the colostomy, the tempera-

ture continued from 101° to 104° F, the pulse ranged from 130 to 150, but the abdominal distention was relieved. He drained about 1,500 cc of thick, dark urine from the suprapubic tube daily. Three days after the colostomy, the patient presented the picture of beginning uremia, with twitching of the extremities. The blood urea, which had come down to 15 mg per 100 cc after the suprapubic cystotomy, rose to 40 mg. The patient died four days after the colostomy.

Autopsy—Upon opening the sigmoid, an obstruction was found about ten inches proximal to the rectosigmoid junction. Here the wall of the sigmoid was markedly thickened. The sigmoid was firmly attached at this point to the underlying structures. At the rectosigmoid, the wall of the bowel was again thickened and the lumen stenosed. There was multilocular abscess which extended along either side of, and posterior to, the sigmoid, and continued down around the rectum, so that the rectum lay as an isolated tube in the midst of an abscess. The abscess involved the perisigmoidal and perirectal tissues, and communicated with the fundus of the bladder by an opening about 2 cm in diameter, and with the prostate by a sinus through the periprostatic tissues. The walls of the abscess were necrotic. At the point of marked obstruction of the sigmoid there were many diverticula, a few of which had perforated into the large perisigmoidal abscess. The other findings were a gangrenous cystitis, ascending pyelonephritis, chronic peritoneal adhesions, and tension ulcers of the ileum and cecum.

CARCINOMA ASSOCIATED WITH DIVERTICULITIS

Case 19—Hosp No 379596 A H, female, age 65, was admitted to the hospital, May 8, 1935, with the history of left lower quadrant abdominal pain of 20 years' duration, and diarrhea of seven years' duration. The pain had been severe for eight days prior to admission. The patient had been in the hospital three years before, at which time a diverticulosis of the colon had been demonstrated. Temperature 101.8° F. The abdomen was distended and there was a firm, tender mass in the left lower quadrant. On rectal examination, a hard, tender mass could be felt extending up the left pelvic wall. Leukocytes 23,200, 92 per cent polymorphonuclears. The patient was treated conservatively for two weeks, during which time the pelvic mass, felt on rectal examination, grew larger.

Operation—Gas-oxygen-ether anesthesia. A large abscess in the left lower quadrant of the abdomen was found and drained. The patient died two days after operation.

Autopsy—The peritoneum in the lateral gutters, from the pelvis to the diaphragm, was covered by a fibrinous exudate, and filled with turbid fluid. Pockets, produced by adhesions of loops of small intestine, were filled with the same character of fluid. The mucosa of the rectosigmoid, and of the sigmoid, for a distance of 6 cm proximal to this, was the seat of a completely annular, cauliflower-like, ulcerating tumor. The wall of the sigmoid in this area was diffusely indurated. One-half centimeter proximal to the tumor, on the lateral wall of the sigmoid there was a perforated diverticulum with a surrounding perisigmoidal abscess. The serosal aspect of the sigmoid and the portion of the genital tract forming the perisigmoidal abscess were markedly discolored and covered with exudate. There were two large duodenal diverticula. There were many diverticula throughout the colon containing inspissated fecal material. The pathologic report of the tumor was adenocarcinoma with lymph node metastases.

SUMMARY

In the ten-year period, 1927-1937, 35 cases of diverticulitis of the colon were admitted to the Surgical Services of the Mount Sinai Hospital. Surgical complications were present in 19 of these cases, and 16 cases were uncomplicated. The complications consisted of peritonitis without perforation in two cases, perforation with abscess in five cases, perforation with peri-

DIVERTICULITIS OF THE COLON

tonitis in five cases, peridiverticulitis (stenosis) in four cases, sigmoidovesical fistula in two cases, and associated carcinoma in one case

There was a marked difference in the age groups of the two types of cases as shown in Table II

TABLE II

Type	0-10 Years	10-20 Years	20-30 Years	30-40 Years	40-50 Years	50-60 Years	60-70 Years	70-80 Years	80-90 Years	Average Years
Uncomplicated cases	0	0	0	0	0	2	7	6	1	69
Complicated cases	1	0	1	5	3	5	2	2	0	51

A case of diverticulitis of the colon in an 18-hour-old infant was reported, which is the youngest case on record

The symptoms in the uncomplicated cases were, in the order of frequency, lower abdominal pain constipation, diarrhea, blood in stools, and vomiting. The symptomatology in the complicated cases was determined by the type of complication present. Positive findings were not always found on physical examination in the uncomplicated cases, but the diagnosis of diverticulitis was confirmed roentgenologically. In the complicated cases, the findings on physical examination were those of the complication present in the individual case. The sigmoid was the most frequent site of disease, but in two cases there was a perforation of a diverticulum of the splenic flexure of the colon.

The uncomplicated cases were not operated upon, and subsided under conservative therapy. The operative mortality in the cases with surgical complications was high—62 per cent. The salient facts in the fatal cases give some of the reasons for this high mortality.

There was one death in the two cases with peritonitis without perforation. This patient had a diffuse peritonitis of eight days' duration. There were three deaths in five cases with perforation and abscess. In the first case, a Mikulicz exteriorization in addition to the drainage of the abscess was performed. A gangrenous inflammation of the abdominal wound and the tissues surrounding the operative site contributed to the fatal issue. The remaining two patients were in poor condition, with large, multilocular abscesses, in whom the drainage of the abscesses did not influence the course of the disease.

There were four deaths in the five cases with perforation and peritonitis. These patients had advanced, diffuse peritonitis. Two of these patients were so toxic that operation was not performed. The third death was that of the 18-hour-old infant. The fourth patient was operated upon within a few hours of admission without adequate preoperative therapy. There were two deaths in the four cases with peridiverticulitis. One patient had an advanced intestinal obstruction. He refused operation, and died the day following admission. The other patient had a primary resection of the sigmoid with an end-to-end anastomosis. There was no autopsy, but there were clinical evidences of peritonitis. The two patients with sigmoidovesical

fistulae died. One patient had a primary resection of the sigmoid with an end-to-end anastomosis. Death was due to leakage of the suture line and peritonitis. The other patient had advanced perisigmoidal suppuration. The patient with associated carcinoma died of a peritonitis secondary to the perforation of the diverticula of the sigmoid.

The cases in this paper were from the surgical services of Drs. Edwin Beer, Albert A. Berg, Ralph Colp, Charles A. Elsberg, Richard Lewisohn, Alexis V. Moschcowitz and Harold Neuhoef. The author wishes to express his appreciation to these heads of services for the use of these cases.

BIBLIOGRAPHY

- ¹ Brewer, G. E. The Etiology of Certain Cases of Left-Sided Intra-Abdominal Suppuration—Acute Diverticulitis. *Am Jour Med Sci*, **134**, 482, 1907.
- ² Brown, P. W., and Marcle, D. M. Prognosis of Diverticulitis and Diverticulosis of the Colon. *J A M A*, **109**, 1328, 1937.
- ³ Bryan, R. C. Sigmoidovesical Fistula. *ANNALS OF SURGERY*, **63**, 353, 1916.
- ⁴ Cameron, H. C., and Rippman, C. H. Five Cases in Which Acquired Diverticula of the Colon Led to Death. *Guy's Hosp Rep*, **64**, 373, 1910.
- ⁵ Conway, F. M., and Hitzrot, J. M. Diverticulitis of the Colon. *ANNALS OF SURGERY*, **94**, 614, 1931.
- ⁶ Edwards, H. C. Diverticulitis. A Clinical Review. *Brit Med Jour*, **1**, 973, 1934.
- ⁷ Eggers, C. Diverticulitis and Sigmoiditis. *ANNALS OF SURGERY*, **94**, 648, 1931.
- ⁸ Fallon, J. Discussion of D. F. Jones's¹³ paper. *New Eng Jour Med*, **203**, 469, 1930.
- ⁹ Fiedler, H. The Pathological Significance of Diverticula of the Colon. *Deutsch Ztschr d Ges f Nat u Heilk*, Dresden, 1868.
- ¹⁰ Fifield, L. R. Diverticulitis. *Lancet*, **1**, 277, 1927.
- ¹¹ Foggie, W. F. Diverticulitis with Metastatic Suppuration. *Lancet*, **1**, 1357, 1921.
- ¹² Jaboulay. Quoted by Regnier. Sigmoiditis. *These de Lyon*, **48**, 1898.
- ¹³ Jones, S. Communication between the Sigmoid Flexure and Bladder, the Result of Ulceration of a False Diverticulum. *Trans Path Soc, London*, **10**, 131, 1859.
- ¹⁴ Judd, E. S., and Pollock, L. W. Diverticulitis of the Colon. *ANNALS OF SURGERY*, **80**, 425, 1924.
- ¹⁵ Kellogg, W. A. Vesico-Intestinal Fistula. *Am Jour Surg*, **41**, 135, 1938.
- ¹⁶ Kramer, S. E., and Robinson, W. Acquired Suppurative Diverticulitis with Pylephlebitis and Metastatic Suppuration in the Liver. *Surg, Gynec and Obstet*, **42**, 540, 1926.
- ¹⁷ Lett, H. Vesicocolonic Fistulae. *Proc Roy Soc Med*, **25**, 1811, 1932.
- ¹⁸ Lockhart-Mummery, J. P. Discussion of Lett's¹⁷ paper.
- ¹⁹ Loomis, A. L. Peritonitis Due to False Diverticula. *New York Med Rec*, **4**, 497, 1870.
- ²⁰ Mayo, W. J., Wilson, L. B., and Giffin, H. Z. Acquired Diverticulitis of the Large Intestine. *Surg, Gynec and Obstet*, **5**, 8, 1907.
- ²¹ McGrath, B. F. Intestinal Diverticula, Their Etiology and Pathogenesis. *Surg, Gynec and Obstet*, **15**, 429, 1912.
- ²² Monsarrot, K. W. The Surgical Treatment of Diverticulitis. *Brit Med Jour*, **2**, 41, 1928.
- ²³ Newton, F. C. Acquired Diverticula of the Colon. *Arch Surg*, **18**, 1339, 1929.
- ²⁴ Nitch, C. A. R. Discussion of Lett's¹⁷ paper.
- ²⁵ Parham, F. W., and Hume, J. Vesico-Intestinal Fistulae. *ANNALS OF SURGERY*, **50**, 251, 1909.
- ²⁶ Patel, M. Perforating Sigmoiditis with Generalized Peritonitis. *Lyon Chir*, **6**, 121, 1911.

- ²⁷ Rankin, F W , and Brown, P W Diverticulitis of the Colon Surg , Gynec and Obstet , 50, 836, 1930
- ²⁸ Sutton, G D Vesicosigmoid Fistulae Surg , Gynec and Obstet , 32, 318, 1921
- ²⁹ Telling, W H M Acquired Diverticula of the Sigmoid Flexure Lancet, 1, 843, 1908
- ³⁰ Telling, W H M , and Gruner, O C Acquired Diverticula, Diverticulitis and Peridiverticulitis of the Large Intestine Brit Jour Surg , 4, 468, 1917
- ³¹ Whyte, J M A Case of Suppurative Hepatitis Following Inflammation in an Acquired Diverticulum of the Sigmoid Scot Med and Surg Jour , 18, 120, 1906

THE PRODUCTION OF HYPER- AND HYPOMOTILITY OF THE MUSCULATURE OF THE SMALL BOWEL IN THE HUMAN

EXPERIMENTAL STUDIES ON THE

(A) NORMAL PERISTALTIC ACTIVITY

(B) EFFECT OF MORPHINE

(C) EFFECT OF ATROPINE

ARMAND C FORSTER, M D

ST LOUIS, MO

FROM THE DEPARTMENT OF SURGERY, ST LOUIS UNIVERSITY SCHOOL OF MEDICINE, ST LOUIS, MO

ADVANTAGE was taken of a case of intestinal prolapse or bowel exteriorization (involving the lower one-third of the ileum) in an otherwise healthy male to record daily circular and longitudinal muscle activity of the exposed bowel. The loop of exteriorized ileum was 12 inches in length with an artificial anus at its summit so that the lower limb of the loop was constantly empty. The method of recording, described by Alvarez,¹ was adapted in the following manner. Two Wiggers myocardiographs were fastened to four permanent nonabsorbable sutures loosely encircling a mass of circular or longitudinal muscle, as is shown in Fig 1. The longitudinal fibers selected were on the antimesenteric border of the limb of the loop traversed by intestinal contents. The sutures that encircled these were approximately two and one-half inches apart. The bundle of circular fibers selected crossed these at about their middle and the sutures around these were about one and one-half inches apart. Rubber tubes were used to transmit variations in pressure from the receiving myograph to a recording tambour of the fall away lever type. A watch timer was used to record time in six-second intervals, and also to serve as a base line. The apparatus was so arranged that it could be set up in working order at the bedside of the patient without changing his position and might be used with the patient in either a lying or semisitting position.

Continuous kymographic tracings were thus taken daily from the same segment of exposed lower ileum before, during, and after the administration of pharmacopoeal and clinical doses of a drug. The "normal" peristaltic activity during the preinjection period served as a satisfactory basis for comparison of pharmacodynamic effects on intestinal muscle.

The effects recorded were also visually observed with regard to expulsion of intestinal contents from the visible anus and could be correlated with propulsive and nonpropulsive intestinal movement.

The following general precautions were observed in all experiments. The patient was prepared in no way for the experiment with the exception that any medication he might have been taking was discontinued the night

before All experiments were conducted two hours following meals To obviate reactions to the mechanical stimulus, tracings were not taken until at least 20 minutes after attachment of the myographs to the sutures in the bowel The experiment was usually discontinued when the patient began to

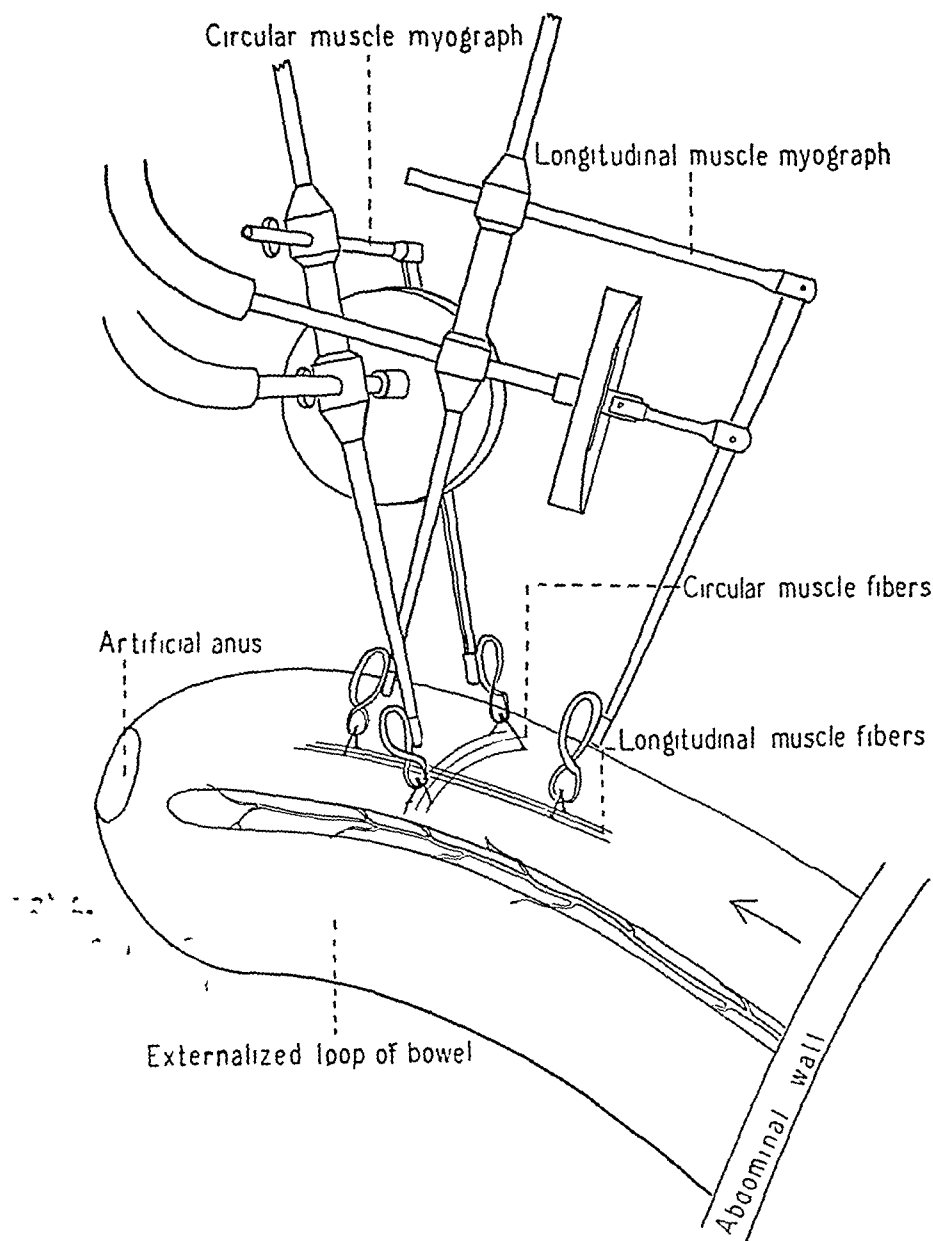


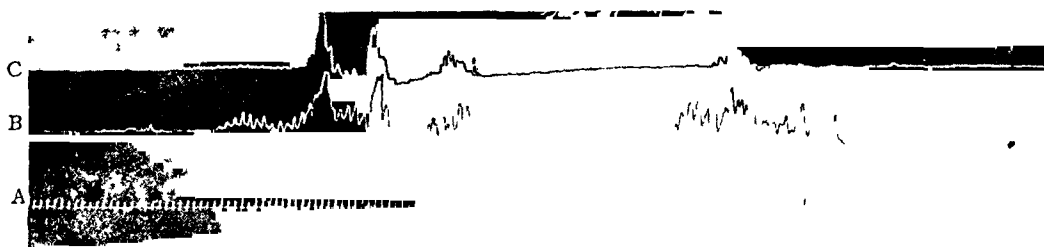
FIG 1—Illustrates schematically, the set up employed to register the motor activity of the musculature of the small intestine

complain of pain or fatigue During the experiment, the exposed bowel was kept covered with saline pledgets and a rubber dam to prevent evaporation A 75-watt drop light maintained external heat

RESULTS—“Normal” Peristaltic Activity It was noted in a study of the first 20 to 30 minutes of each experiment that there were periods of activity and periods of inactivity, and that during the periods of activity certain contractions were effective in producing a forceful expulsion of intestinal contents For the period of activity to be most effective in producing propulsion

we noted that both muscle coats worked simultaneously but the onset of longitudinal muscle contraction preceded that of circular muscle contraction by from one to one and one-half minutes and continued after contractions in the circular muscle had ceased. That is to say that the duration of longitudinal muscle contraction was always greater than the period of circular muscle contraction. We, therefore, refer to this series of synchronous contractions as the "peristaltic" wave. Two such peristaltic waves are shown in Graph 1. This wave occurred normally one to six times during a 30-minute preinjection period and had an average duration of from one to six minutes.

All other intestinal activity not effective in causing propulsion we classified as the "mixing" wave. These are single contractions followed by equal phases of relaxation with an average duration of six to 12 seconds each. In our records this wave appeared normally nine to 150 times during a 30-minute period.



GRAPH 1 —Showing "normal" intestinal activity
Key —A Base line and time in six second intervals
B Longitudinal muscle contraction
C Circular muscle contraction

In the records, changes in either circular or longitudinal muscle tone are shown by increase or decrease of either writing line from the base line (Graph 1). An increase in this distance (A-B, or A-C) represents an increase in muscle tone.

Experiments were made with morphine sulphate, atropine sulphate, pilocarpine hydrochloride, pituitrin, pitressin, prostigmin, Hartmann's solution, and 5 per cent glucose.

Effect of Morphine Sulphate —There are four experiments undertaken to show the effects of the intramuscular injection of morphine sulphate. The morphine was given into the deltoid muscle two hours following a regular hospital meal. The dose was gr $\frac{1}{8}$, followed in 20 to 30 minutes by gr $\frac{1}{8}$. In two of the four experiments a third injection of gr $\frac{1}{8}$ of morphine was given (Table 1).

Intestinal activity before and after morphine administration was recorded in Experiment III as shown in Graph 2. In all experiments a complete suppression of propulsive activity followed morphine gr $\frac{1}{8}$. The frequency of the "mixing" wave was increased in all experiments. The first effects appeared two to four minutes following administration. Circular muscle tone was slightly increased in Experiments I and IV but remained unchanged in

MOTILITY OF SMALL INTESTINE

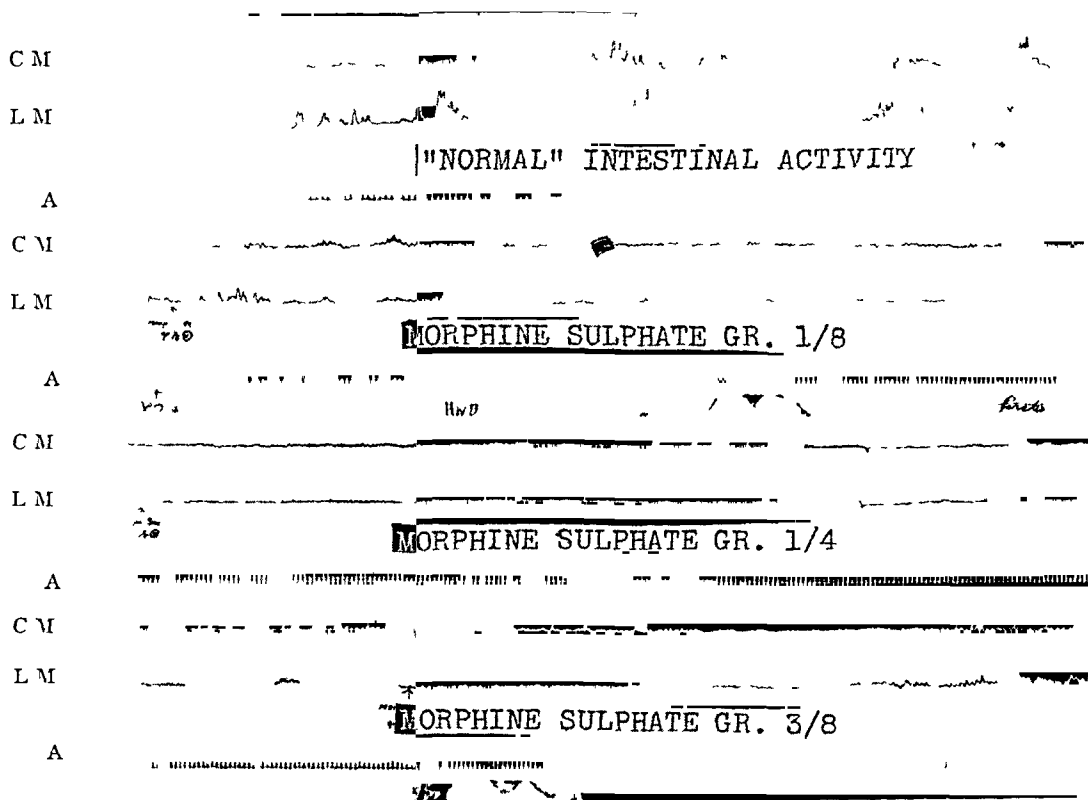
TABLE I

Experiment I				Experiment II				Experiment III				Experiment IV												
Circular Muscle	Height of Contraction in Centimeters	Duration of Contraction in Minutes	Height of Contraction in Centimeters	Normal	Morph Gr	Sulph $\frac{1}{8}$	Morph Gr	Sulph $\frac{1}{4}$	Normal	Morph Gr	Sulph $\frac{1}{8}$	Morph Gr	Sulph $\frac{1}{4}$	Morph Gr	Sulph $\frac{3}{8}$	Normal	Morph Gr	Sulph $\frac{1}{8}$	Morph Gr	Sulph $\frac{1}{4}$				
				0 60	0 70	0 00	0 00	1 70	1 30	0 00	0 00	0 00	0 00	0 70	1 40	1 40	1 50	0 00	0 00	0 00	0 40	0 30	0 00	0 00
				4 20	3 00	0 00	0 00	1 06	1 06	0 00	0 00	0 00	0 00	3 00	5 40	1 30	1 30	0 00	0 00	0 00	3 00	3 42	0 00	0 00
				1 40	1 20	0 00	0 00	1 60	1 10	0 00	0 00	0 00	0 00	1 60	1 70	1 60	1 40	0 00	0 00	0 00	1 20	1 00	0 00	0 00
Longitudinal Muscle	Duration of Contraction in Minutes	Number of Peristaltic Waves During 30 Minutes	Number of Mixing Waves During 30 Minutes	4 24	3 48	0 00	0 00	3 00	2 10	0 00	0 00	0 00	0 00	3 12	6 12	2 00	1 40	0 00	0 00	0 00	4 06	4 30	0 00	0 00
				3	3	0	0	6	6	0	0	0	0	6	6	6	6	0	0	0	3	3	0	0
				28	27	180	40	9	9	195	150	195	30	30	30	30	180	160	120	50	50	100	80	
				Minutes that longitudinal muscle contraction precedes contraction of the circular muscle (peristaltic wave)																				
Time in minutes for the circular muscle to regain tone following the peristaltic wave				0 36	1 06	0 00	0 00	1 06	1 30	0 00	0 00	0 00	0 00	0 24	0 30	0 24	0 18	0 00	0 00	0 00	0 54	0 30	0 00	0 00
Time in minutes for the longitudinal muscle to regain tone following the peristaltic wave				3 06	2 00	0 00	0 00	1 12	1 18	0 00	0 00	0 00	0 00	1 12	1 00	0 00	1 00	0 00	0 00	0 00	0 12	0 00	0 00	0 00
Loss in Tone—Circular Muscle				1 00	3 45	0 00	0 00	1 24	1 24	0 00	0 00	0 00	0 00	2 30	1 30	0 00	1 12	0 00	0 00	0 00	1 00	0 54	0 00	0 00
Loss in Tone—Longitudinal Muscle				Inc	Inc	Inc	Inc	Same	Inc	Inc	Inc	Inc	Inc	Inc	Inc	Inc	Inc	Inc	Inc	Inc	Inc	Inc	Inc	Inc

Experiments II and III Longitudinal muscle tone remained unchanged in the first two experiments but was increased in Experiments III and IV by morphine gr $\frac{1}{8}$

In all experiments a second dose of gr $\frac{1}{8}$ decreased the frequency of the "mixing" wave and increased the muscle tone of both coats

When a total of three gr $\frac{1}{8}$ doses of morphine had been given the frequency of the "mixing" wave was increased in Experiment II from 150 to 195, and decreased in Experiment III from 160 to 120



GRAPH 2—Showing the effect of the injection of a varying dosage of morphine sulphate (Gr $\frac{1}{8}$ — $\frac{1}{4}$ — $\frac{3}{8}$) in comparison with the "base line" graph showing the "normal" intestinal activity

Key—C M Circular muscle contraction
L M Longitudinal muscle contraction
A Baseline and time in six second intervals

Effect of Atropine Sulphate—Gram $\frac{1}{150}$ atropine sulphate was given subcutaneously in four experiments and tracings were taken in the manner described, approximately two hours following the midday meal

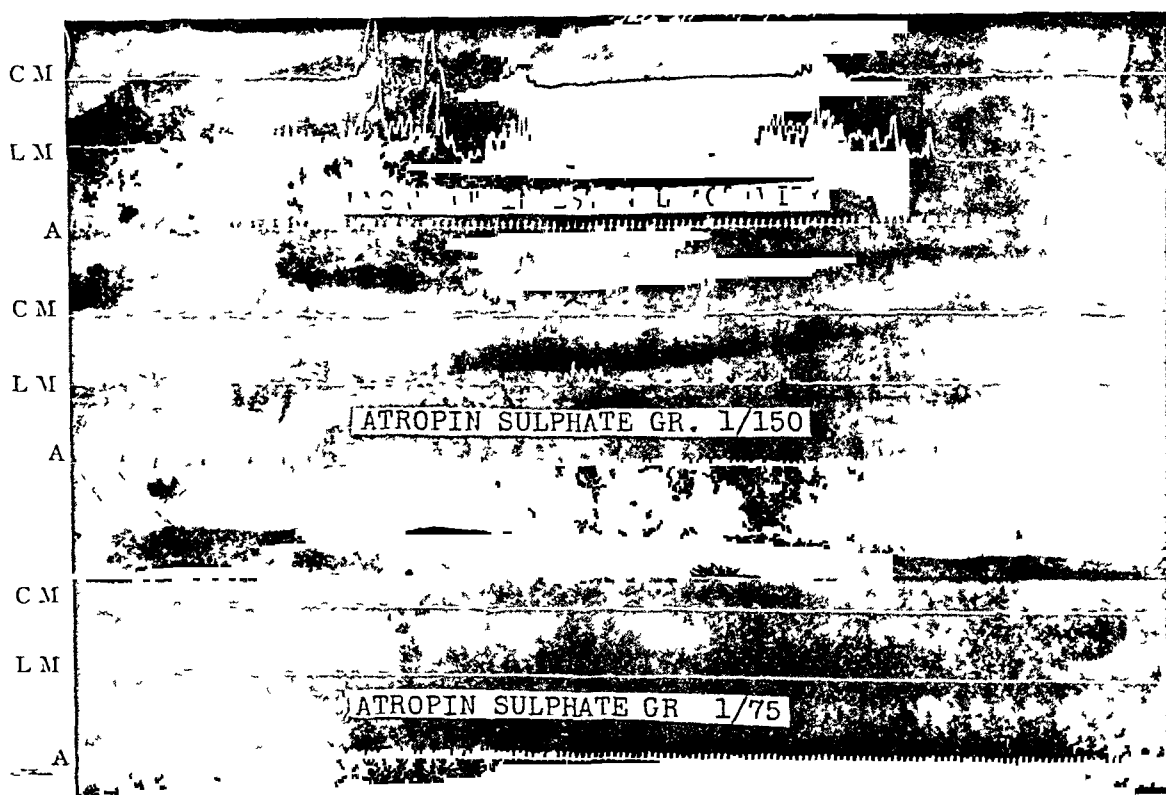
In all four experiments propulsive and nonpropulsive activity was decreased following gr $\frac{1}{150}$ atropine sulphate. Intestinal activity before and after atropine administration was recorded in Experiment IV as is shown in Graph 3

In Experiment IV, two peristaltic waves were recorded during the pre-injection period. The atropine was then given, and, from there on, a complete suppression of all propulsive activity ensued (Graph 3). In Experiment I, the frequency of the peristaltic wave was decreased from six to three,

in Experiment II, from five to two, and in Experiment III, from three to zero by gr 1/150 atropine sulphate

In all experiments there were no peristaltic waves recorded following the second injection of gr 1/150 atropine

In all experiments, circular muscle tone remained unchanged following either the first or second injection of atropine. Loss of longitudinal muscle tone was demonstrated in two experiments to follow the second injection of atropine



GRAPH 3 —Showing the effect of the injection of a varying dosage of atropine sulphate (Gr 1/150-1/75) in comparison with the "baseline" graph showing the "normal" intestinal activity

Key —C M Circular muscle contraction
L M Longitudinal muscle contraction
A Baseline and time in six second intervals

Discussion —Whether our observations truly record the action of circular or longitudinal muscle alone, may be questioned. One is well aware that the circular muscle is not strictly circular nor is the longitudinal strictly longitudinal, but rather that their fibers intermingle and deviate more or less from the coronal or sagittal planes of the intestine in which they happen to lie. Such variations, however, may be ignored and the record of their action, as shown here, may be taken to represent that of the circular and longitudinal muscle in the wall of the human, exteriorized small bowel loop.

As regards the relations between the two muscle coats during a peristaltic movement, Van Braam Houckgeest,² in 1872, observed that the advancing ring of constriction in a peristaltic movement was immediately preceded by a shortening of the longitudinal muscle fibers. Bayliss and Starling,³ in 1901, observed that both muscle coats were affected in the contraction above and relaxation below. Krishnan,⁴ in studying the peristaltic action of cats,

in 1932, concluded that In a peristaltic movement, a wave of longitudinal muscle contraction with relaxation of the circular muscle preceded a wave of circular muscle contraction with relaxation of the corresponding longitudinal muscle by a full wavelength. Our findings in man were the same as those observed by Krishnan in the cat except that we found the interval of time between the onset of contraction of both muscle coats to vary between one-half to one and one-half minutes. Contractions of the longitudinal muscle were also found to continue after activity in the circular muscle had ceased.

According to the law formulated by Bayliss and Starling⁵ in the first of a series of three articles of the movement and innervation of the bowel based mainly on balloon records, "excitation of any part of the gut excites contraction above and inhibition below." Langly and Magnus,⁶ in 1905, and Cannon,⁷ in 1912, point out that this myenteric reflex was not always present and often was hard to demonstrate. Alvarez and Mahoney,⁸ in 1924, report that, in a large number of observations, there was a preliminary rise in tone, which was just the opposite of what the law required. Alvarez and Zimmerman,⁹ in 1927, with the help of the motion picture camera, found that if this widening of the bowel did occur it was due to a distention and not to an inhibition. Krishnan, in 1933, states "That, because of the contraction of the longitudinal muscle preceding the peristaltic wave, the gut distal to the wave was shortened and dilated." We were unable to demonstrate, as suggested by Krishnan, the dilatation of bowel before the onset of the peristaltic wave because of the preceding longitudinal muscle contraction, nor were we able to show, in any of our records, an inhibition or dilatation of either muscle coat preceding the peristaltic wave.

Our results following the administration of morphine do not entirely coincide with those of previous investigators. Pancoast and Hopkins,¹⁰ in 1915, concluded, from roentgenologic evidence, that no small intestinal effect followed morphine. In 1926, Plant and Miller¹¹ found that the number of contractions of small bowel seen through a thin-walled hernial sac in man were increased by morphine. Dvorack, *et al*,¹² and Orr and Carlson,¹³ both using the balloon technic of recording, report increased peristaltic activity following small doses of morphine (10 mg). Ori and Carlson further report that large doses of morphine stopped peristaltic activity without altering the frequency of the "mixing" wave. Abbott and Pendergrass,¹⁴ using the intubation tube described by Abbott and Miller, noted that morphine produced, in the upper small bowel, a brief period of stimulation followed by depression, but that frequently the distal coils of ileum did not exhibit any reaction, or merely the phase of depression.

CONCLUSIONS

Activity of the exteriorized lower small bowel in man is either propulsive or nonpropulsive in nature.

The "peristaltic" wave in the lower three feet of the small bowel, effective in producing a propulsion of intestinal contents, occurs one to six times

during 30 minutes, with an average duration of from one to six minutes each. This wave consists of a simultaneous contraction of both muscle coats with the onset of longitudinal muscle contraction preceding that of the circular muscle from one to one and one-half minutes and continuing after contractions of the circular muscle have ceased.

The "mixing" wave is ineffective in causing a propulsion of intestinal contents and consists of single contractions followed by equal phases of relaxation. These waves occur nine to 150 times during 30 minutes with an average duration of from six to 12 seconds each.

Morphine sulphate in gr $\frac{1}{8}$ doses completely suppresses the "peristaltic" wave, but increases the frequency of the "mixing" wave. A second injection of gr $\frac{1}{8}$ morphine, 20 to 30 minutes later, decreases the frequency of the "mixing" wave and increases the tone of both muscle coats.

Grain 1/150 atropine sulphate decreases the frequency of both peristaltic and "mixing" waves. A second injection of atropine, given 20 to 30 minutes later, produces a complete suppression of the "peristaltic" wave, an almost complete absence of the "mixing" wave, and an occasional loss in tone of the longitudinal muscle coat.

REFERENCES

- ¹ Alvarez, W. C. *Mechanics of the Digestive Tract*. 2nd ed., 204, New York, Paul B. Hoeber, Inc., 1928.
- ² Houckgeest, Van Braam. *Untersuchung Uber Peristaltik des Magens und Darmkanals*. *Arch f d ges Physiol*, 6, 266, 1872.
- ³ Bayliss, W. M., and Starling, E. H. *The Movement and Innervation of the Small Intestine*. *Am Jour Physiol*, 26, 125, 1901.
- ⁴ Krishnan, B. T. *Studies on the Function of the Intestinal Musculature*. *Quart Jour Exper Physiol*, 22, 57, 1933.
- ⁵ Bayliss, W. M., and Starling, E. H. *The Movements and Innervation of the Small Intestine*. *Jour Physiol*, 24, 99, 1899.
- ⁶ Langly, L. N., and Magnus, R. *Some Observations of the Movements of the Intestines before and after Degenerative Section of the Mesenteric Nerves*. *Jour Physiol*, 33, 34, 1905.
- ⁷ Cannon, W. B. *Peristaltic Segmentation and the Myenteric Reflex*. *Am Jour Physiol*, 30, 114, 1912.
- ⁸ Alvarez, W. C., and Mahoney, L. J. *Peristaltic Rush in the Rabbit*. *Am Jour Physiol*, 69, 226, 1924.
- ⁹ Alvarez, W. C., and Zimmerman, A. *Absence of Inhibition before Peristaltic Rushes*. *Am Jour Physiol*, 83, 52, 1927.
- ¹⁰ Pancoast, H. K., and Hopkins, A. H. *Effects of Moderate Doses of Some Opium Derivatives on Gastro-Intestinal Tract of Man*. *J A M A*, 65, 2220, 1915.
- ¹¹ Plant, O. H., and Miller, G. H. *Effects of Morphine and Some Other Alkaloids on the Muscle Activity of the Alimentary Canal*. *Jour Pharmacol and Exper Therap*, 27, 361, 1926.
- ¹² Dvorack, H. G., Carlson, H. A., Erickson, T. C., Smith, V. D., and Wangenstein, O. H. *Influence of Morphine on Intestinal Activity in Experimental Obstruction*. *Proc Soc Exper Biol and Med*, 28, 434, 1931.
- ¹³ Orr, T. B., and Carlson, H. E. *Effect of Morphine on the Movements of the Small Intestines and Sphincter Muscles*. *Arch Surg*, 27, 296, 1926.
- ¹⁴ Abbott, W. O., and Pendergrass, E. P. *Intubation Studies of the Human Small Intestine*. *Jour Roentgenol*, 35, 209, 1936.

ADENOMA OF THE ISLETS OF LANGERHANS, WITH HYPER-INSULINISM, ASSOCIATED WITH ADENOMA OF THE THYROID

D P GREENLEE, M D , J G LLOYD, M D , A J BRUECKEN, M D ,

AND

W S McELLROY, M D

PITTSBURGH, PA

FROM THE ST FRANCIS HOSPITAL PITTSBURGH PA

COWLEY,⁶ in 1788, first suggested that the pancreas was disordered in diabetes. In 1869, Langerhans¹⁹ discovered the islet cells in the pancreas, but it was not until 1900 that Ssobolew²³ and Schulze²¹ independently discovered their physiologic significance. Banting³ and his coworkers, in 1922, discovered insulin and shortly after that Seale Harris¹¹ coined the word "hyperinsulinism" and used it to apply to patients in whom there was an abnormally low blood sugar associated with certain symptoms of a more or less definite type, such as one sees from administering too much insulin to diabetics.

The first case of hyperinsulinism due to an islet cell tumor was reported in 1927 by Wilder and W J Mayo.²⁸ This patient was a physician who had a malignant tumor of the islet cells. He was operated upon and eventually died. Biologic assays of the tumor tissue removed definitely proved its insulin activity and correlated perfectly with the clinical phenomena. Roscoe Graham¹³ of Toronto, in 1929, reported the first case of hyperinsulinism cured by surgical removal of an islet cell tumor. Since this original case report, there has been an increasing number of patients operated upon for suspected tumors of the islet cells. Allen O Whipple²⁴ in all probability has operated upon more cases than any other surgeon. Up until a few months ago, he had operated upon 14 cases with two deaths. In every case but one he found one or more adenomata to be present.

The case which is being reported herewith is of unusual interest because the patient is one of the oldest reported having this disorder, and because an adenoma of the thyroid complicated the picture.

Case Report—Hosp No 35—1436 M V, white female, age 56, was admitted to the St Francis Hospital, November 16, 1935, and referred to the Neurologic Service of Dr J G Lloyd on account of episodes of unconsciousness of two and one-half years' duration. The first attack came on while she was in the theater and resembled a fainting seizure. Subsequent to this she suffered from attacks at irregular intervals, usually every seven to ten days at the onset, but becoming progressively more frequent and more severe so that at the time of admission they occurred two to three times a week, and lasted as long as 17 hours. The attacks were most likely to come on in the morning before breakfast. To avert these attacks the patient's daughter had learned to set the alarm at 3 A M and feed her mother.

The mild attacks appeared as simple fainting spells from which the patient recovered rapidly, whereas the severer spells found the patient in deep unconsciousness.

Submitted for publication May 26, 1939

from which she could not be aroused by shaking. At times there was jerking of her extremities during the attack, but for the most part she was limp and relaxed and had involuntary urination and defecation with profuse perspiration. Before becoming unconscious the patient would seem to lose the power of speech and develop a stare, although she was perfectly aware of events preceding her unconsciousness. After an attack the patient usually felt weak and thirsty.

Between attacks the patient appeared perfectly normal at times, but the family could notice a tendency to a personality change, that is, whereas before the patient began suffering from the attacks she was of a cheerful cooperative disposition, as the disorder progressed she showed a tendency to become uncooperative and cantankerous.

The patient knew she had had a goiter for 20 years. About five years prior to admission to the hospital she thought she weighed between 120 and 130 pounds, and she had been losing weight since then. In addition to loss of weight, she complained of heat intolerance, rapid heart action, nervousness and tremor of the hands. The diet of the patient had been restricted during the last two years, particularly as regards meat and carbohydrates.

The rest of the history was irrelevant save for a record several years previously of an attack of severe abdominal pain associated with jaundice. The family physician said she had liver trouble at that time.

Physical Examination—The patient was markedly emaciated, weighing about 80 pounds. Color was fairly good. The patient was edentulous. The thyroid gland was enlarged, particularly in the region of the isthmus and left lobe, where there was a definite adenoma, approximately 4 to 5 cm. in diameter. The patient had a scoliosis of the upper thoracic vertebrae to the right. Heart rate was rapid. Systolic murmurs were present over all valve areas, transmitted to the axilla, A_2 was greater than P_2 . Blood pressure 160/90. No bruit was noted over the thyroid gland. Skin was warm, not particularly moist. A fine tremor of the fingers was present. No abdominal masses were palpable. Pelvic examination showed evidence of atrophic changes in the cervix and vagina. Uterus could not be definitely outlined. Rectal examination was negative. There was moderate quadriceps weakness, but no edema of the legs. Eyegrounds essentially normal.

Laboratory Data—Many laboratory procedures were carried out, the most significant of which were the low blood sugar and high basal metabolic rates. The blood sugar taken November 18, 1935, was so low that it could not be read. A recheck of the blood sugar the following day showed the reading to be 34 mg. A basal metabolic rate taken November 19, 1935, was +54 and a recheck the following day was +65. Urinalysis showed a normal specific gravity and a faint trace of albumin with a few casts and pus cells. Blood count showed hemoglobin of 70 per cent, R B C 3,400,000, W B C 7,300 and an essentially normal differential count. Blood Wassermann and Kahn were negative. Blood chemistry: Calcium 10.9 mg, magnesium 2.9 mg, N P N 28.8 mg, creatinine 1.58 mg.

Roentgenologic examination of the skull was normal. The chest showed evidence of an inactive bilateral tuberculous process. A lateral view showed no evidence of a mediastinal tumor.

It was assumed that the patient had a toxic, adenomatous goiter and hypoglycemia based on the clinical and laboratory data. It was decided to operate upon the thyroid gland first, and she was prepared accordingly, using a high caloric diet with plenty of carbohydrate and Lugol's solution preoperatively. On this regimen the patient seemed to improve and the spells of unconsciousness became less frequent. Nine days after admission to the hospital, she experienced an attack of unconsciousness, and a blood sugar taken at that time was 32 mg. The patient promptly responded to 10 per cent glucose given intravenously. Blood sugars taken on December 2 and December 9, 1935, were reported as nil and 57 mg. respectively. Basal metabolic rates taken on December 2, 5 and 9, 1935, were reported as being +35, +24, and +12 per cent (Chart 1).

The patient's goiter was operated upon December 12, 1935, and a left lobectomy

performed, excising an adenoma about 4 x 5 cm in diameter. The pathologic report, Path No S-2969-35, was cystic adenoma of the thyroid and hyperplasia of thyroid (exophthalmic type).

Subsequent Course—During the course of the operation and for 24 hours postoperatively, 10 per cent glucose in normal saline was administered continuously intravenously. Following this, intravenous glucose was given intermittently postoperatively for an additional 24 hours. The patient made quite a satisfactory convalescence save for one spell of coma about one week postoperatively. At this time her blood sugar was 35 mg. By feeding her coffee and sugar, she quickly responded. She was discharged from the hospital, December 21, 1935, with advice regarding an adequate intake of food, particularly carbohydrates.

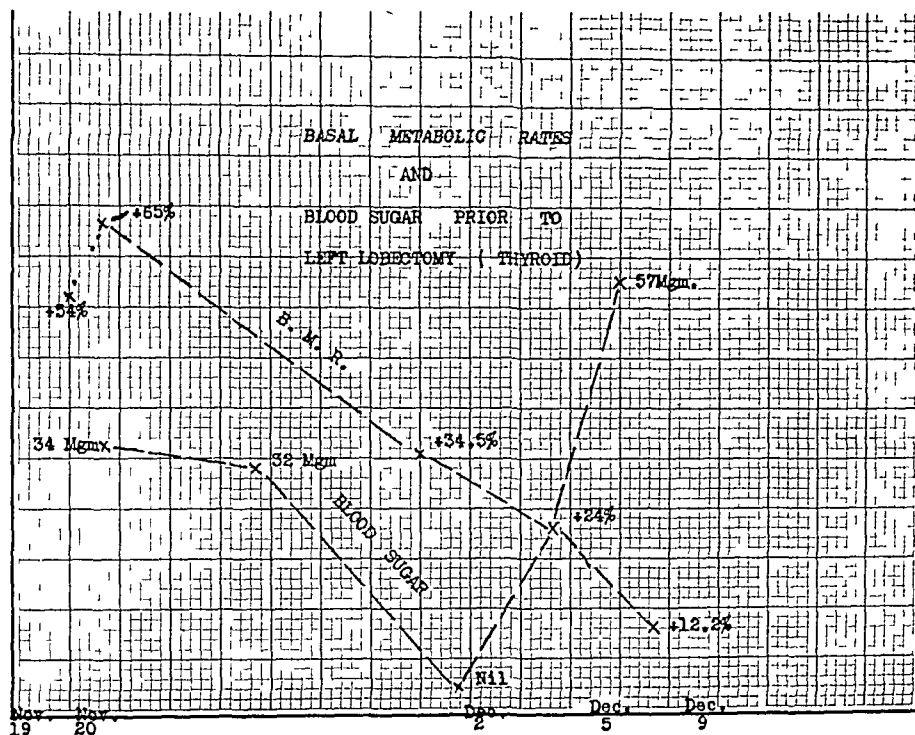


CHART I

She was observed over a period of about a year and showed a marked improvement in her general health with a gain of 30 pounds in weight, and a marked diminution in the number and severity of attacks attributable to the low blood sugar. In over a year she had had only two episodes of complete unconsciousness, but had had several seizures which were averted by the timely administration of sugar.

March 5, 1936 blood sugar 59 mg, basal metabolic rate 22. A sugar tolerance test and basal metabolic rate were determined synchronously, March 7, 1936, with the following results:

Sugar Tolerance Test

57 mg Before ingestion of 80 Gm glucose
218 mg 45 min after ingestion of 80 Gm glucose
280 mg 2 hrs after ingestion of 80 Gm glucose

Basal Metabolic Rates +23 Before ingestion of glucose
+22.5 Taken 1 hr after ingestion of glucose

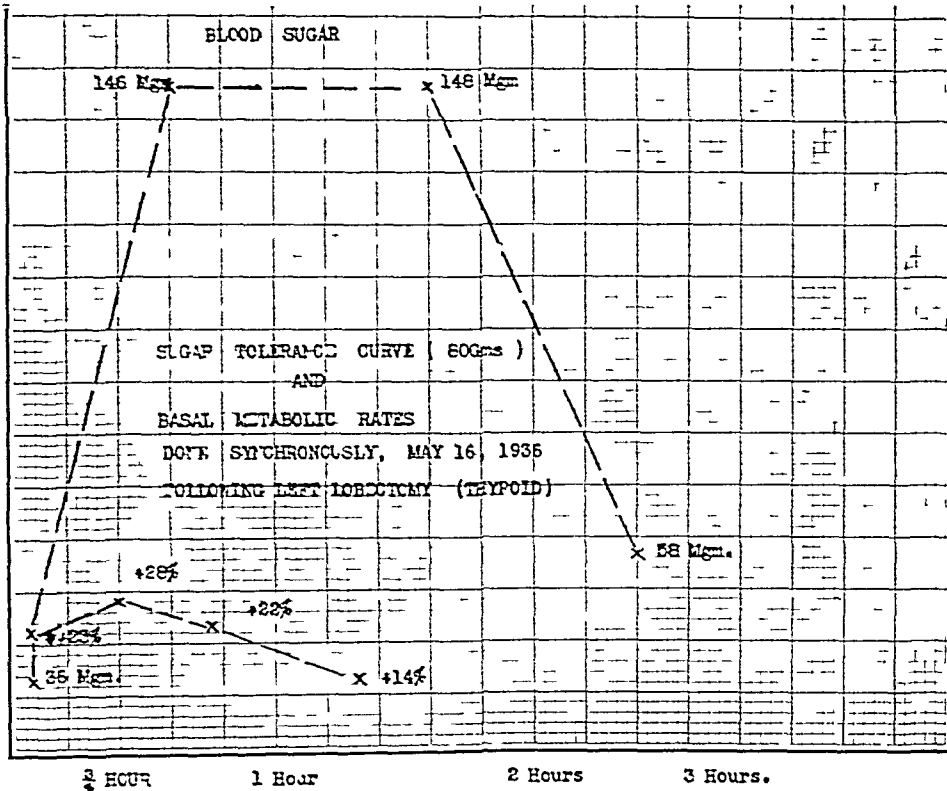
May 16, 1936, she had the same procedure carried out with the following results:

HYPERINSULINISM

Sugar Tolerance Test

Blood Sugar 36 mg Before ingestion of 80 Gm glucose
 146 mg 45 min after ingestion of 80 Gm glucose
 148 mg 2 hrs after ingestion of 80 Gm glucose
 58 mg 3 hrs after ingestion of 80 Gm glucose

Basal Metabolic Rates +22.8 Before ingestion of 80 Gm glucose
 +27.4 ½ hr after ingestion of 80 Gm glucose
 +22.5 1 hr following the above
 +14.2 ¾ hr following the above (Chart 2)



August 20 1936 Blood sugar 35 mg In view of the incomplete relief of the symptoms the patient was readmitted to the hospital Hosp No 55582, January 27, 1937 for exploration of the pancreas Diagnosis Adenoma of islets of Langerhans

January 28, 1937 Blood sugar 25 mg basal metabolic rate —1 On February 1, 1937 the pancreas was explored giving full glass of orange juice and one ounce of sugar three hours preoperatively to the patient The operative note follows

Operation—Dr D P Greenlee Under ethylene-ether anesthesia a high left rectus incision was made The pancreas was explored by opening through the gastrocolic omentum A tumor about 1½ cm in diameter was found situated in the body of the pancreas near its junction with the tail lying close to the inferior border This was removed by placing clamps on either side of the tumor and removing a wedge shaped piece of pancreas Bleeding was controlled by using a running mattress suture The splenic vein was visualized at the posterior upper border of the pancreas A cigarette drain was introduced down where the tumor had been removed from the pancreas The rent in the gastrocolic omentum was sutured The gallbladder contained at least one gallstone and there was moderate associated hepatitis Exploration of the rest of the upper abdomen was negative and the remainder of the pancreas was explored and no

further tumors found. At the start of operation a continuous venoclysis of 10 per cent glucose in normal saline was started, and this was used throughout operation.

Pathologic Examination—*Gross* Path No S-221-37, Dr A J Bruecken. The specimen consisted of a tumor and pancreatic tissue from the inferior portion of the pancreas, and measured $2.8 \times 2.0 \times 1.8$ cm over all. The surface had a thin connective tis-

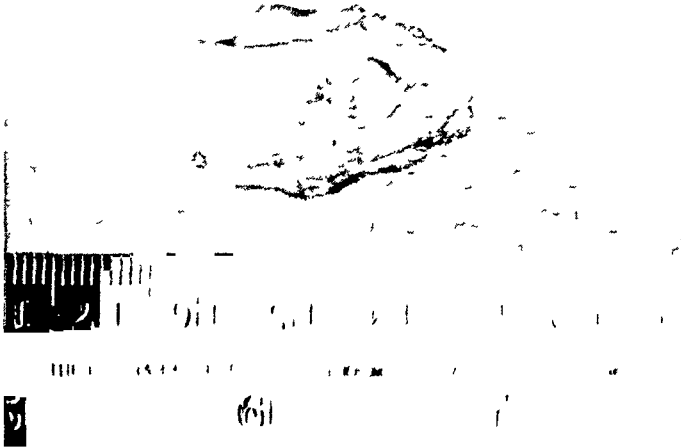


FIG 1—Gross appearance of specimen

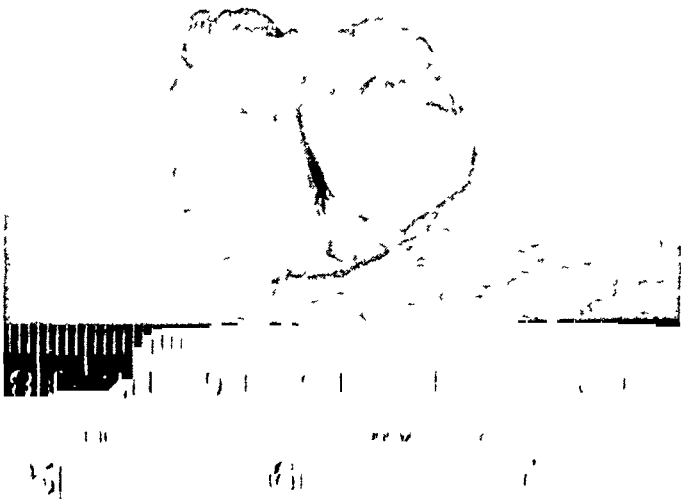


FIG 2—Cut section of tumor

sue covering, slightly blood stained. Beneath this, the tissue had a light, brownish-yellow, lobulated appearance. Three-fourths of the circumference of the specimen had a ragged edge while the remainder had a smooth, regular margin. On palpation, there was a central round area of quite firm consistency, surrounded by soft, meaty pancreatic tissue, this central firm area was not visible on the surface, being completely enclosed by pan-

creatic tissue On section, there was found to be a firm, yellowish-gray, somewhat fibrous and faintly granular appearing, definitely encapsulated, rounded tumor mass which measured $1.7 \times 1.5 \times 1.2$ cm The cut-surface was smooth and greasy At one side of the tumor there was a small area showing several pinpoint-sized, red areas resembling hemorrhage within the tumor Surrounding the tumor was brownish-yellow pancreatic tissue showing the usual glandular appearance The greater portion of the tumor lay 2 Mm beneath the surface of the pancreas, this 2 Mm was composed of pancreatic tissue with its external, thin fibrous membrane The entire specimen weighed 3.5 Gms The tumor was intact and could be easily shelled out of its capsule (Figs 1 and 2)

Microscopic Section of the mass with surrounding pancreatic tissue showed the latter and a marked dilation of the large duct in it The mass showed

a definite capsule of fibrous tissue separating it from the surrounding pancreatic tissue for only a part of its extent In the other part, while the lobules of the growth were each surrounded by a fibrous capsule and distinct, nevertheless they were located directly within the acinar lobules of the pancreatic tissue, and furthermore a few isolated acini

of the latter extended into the growth for a short distance The growth was composed of irregular masses of cells which varied greatly in size and in the amount of surrounding connective tissue The largest mass bore some resemblance to a markedly hyperplastic thyroid nodule and there was marked retraction of the stroma processes with a very abundant blood supply and no evidence of necrosis The rounded portions of the growth distinctly recalled islets of Langerhans, but some of the larger formations suggested a papillary, adenomatous structure, and in fact one could easily demonstrate a glandular tubule and rarely some inspissated secretion in such a tubule The cells were sometimes arranged in a continuous mass or column without stroma partitions which produced a pseudoglandular appearance elsewhere The

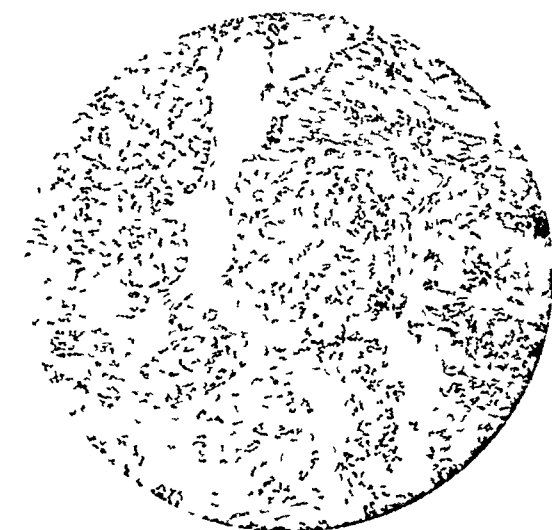


FIG 4—Low power—showing relation of tumor to acinar pancreatic tissue in upper left Islands of tumor cells in lower portion, with increase of vascular stroma on the right

cells appeared fairly uniform but there were some distinct variations With the present H & E stain they appeared compact, polygonic, medium-sized with round or oval nuclei showing small nucleoli and in general not unlike greatly enlarged dense islet cells or simple columnar epithelium of the ducts The adjacent islets showed much smaller cells There was also a distinct tendency in places to form a regular basal row of cells like lining epithelium Under the capsule-like structure between the adherent pancreatic tissue and the growth there was a very marked replacement of the tumor cells by fibrous tissue This recalled receding mammary lobules There was, therefore, a distinct intermingling

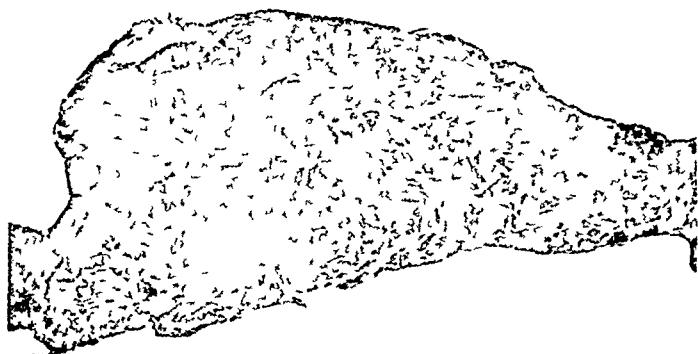


FIG 3—Very low power—showing surrounding pancreatic tissue on the left and scirrhous type of growth on the right

between the growth and surrounding pancreatic tissue but only at the margins. Nowhere else could one find pancreatic tissue within the confines of the growth. The large amount of collagenous stroma in the growth was noteworthy. Further study revealed a considerable number of structures resembling ducts with quite tall epithelial cells. There were a considerable number of cells with large, and sometimes irregular, nuclei and with prominent nucleoli which were basophilic, and rarely a definite mitotic figure was encountered. Inflammatory cell infiltration was entirely absent save for a very few lymphocytes at one or two points in the stroma.

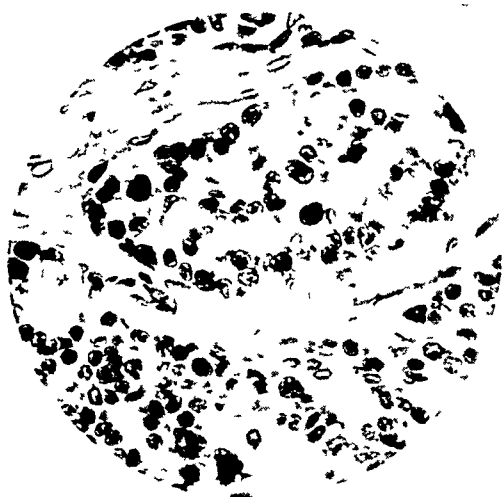


FIG 5—High power—showing resemblance to islet tissue and intimate relation to capillary blood vessels lined more or less by tumor cells. Pronounced polymorphism and mitosis of cells.



FIG 6—Tubular formations intimate relation to capillaries, more uniformity and inspissated secretion in tubule in uppermost portion.

Another section showed a still more scirrhus picture, with a heavy stroma equaling the glandular tumor tissue. Rarely a giant cell with several large deeply staining nuclei was seen above or within a cell mass. The cells of the growth appeared larger than any of the surrounding pancreatic tissue, namely, acinar, islet and duct cells. They may have represented overgrowth of the small connecting tubes of the organ.

E & M stain brought out the variations in the characters of cells of the growth more conspicuously and this, together with the irregularity of the masses and the great amount of stroma, suggested unrestricted aberrant growth.

Sections stained by Goodpasture's granular stain after Orth's fixation showed what appeared to be poorly staining mitochondria, and comparing the staining affinity with the surrounding pancreatic islets the tumor cells most nearly resembled *beta* cells taking more blue than red color but showing no definite granules which, however, was not shown in the surrounding islands (Figs 3, 4, 5 and 6).

Biologic assays of the tumor tissue were made by Dr W S McEllroy, with the following results:

Total weight of tumor tissue	0.95 Gm	{ Method of Scott and Best used in extraction Control (Starved 36 hrs)
Total volume of extract from	= 10 cc	
Vol extract injected = 5 cc = 0.475 Gm tissue		
	Rabbit Injected (Starved 36 hrs)	
Time		
11 40 A M.	Blood sugar 0.083 mg	Blood sugar 0.106 mg
11 45 A M	Injected 5 cc of extract	
1 07 P M	Blood sugar Nil	Blood sugar 0.132 mg
	Rabbit in shock with convulsions	

HYPERINSULINISM

1 15 P M	Injected 5 cc 10% dextrose intramuscularly	
1 30 P M	Rabbit able to partially sit up	
1 42 P M	Blood sugar Nil	Blood sugar 0 115 mg
1 45 P M	5 cc glucose 10% intravenously	
2 27 P M	Blood sugar Nil	

Rabbit injected showed fall in blood sugar with shock and convulsions which were relieved by glucose. Rabbit after intravenous glucose showed rapid improvement and by the next morning behavior was normal.

The reaction induced by injection of material from 0.475 Gm of tissue believed to be a typical insulin effect.

The patient made an uneventful convalescence from operation save for moderate ileus for a few days postoperatively. The drain was removed on the sixth postoperative day. There was some serous drainage from the wound for about 11 to 12 days following removal of the cigarette drain, but at no time did it produce skin irritation, and chemical study failed to reveal pancreatic enzymes. Blood sugar determinations were made on the third and seventeen days post operatively and were found to 179 mg and 94 mg respectively. A blood sugar determination made about five weeks after operation was 95 mg.

Since operation the patient has been completely relieved of her symptoms, and a sugar tolerance test, performed May 13, 1937, showed

101 mg	before ingestion of glucose
202 mg	45 min after ingestion of 100 Gm glucose
210 mg	2 hrs after ingestion of 100 Gm glucose
148 mg	3 hrs after ingestion of glucose
86 mg	4 hrs after ingestion of glucose (Chart 3)

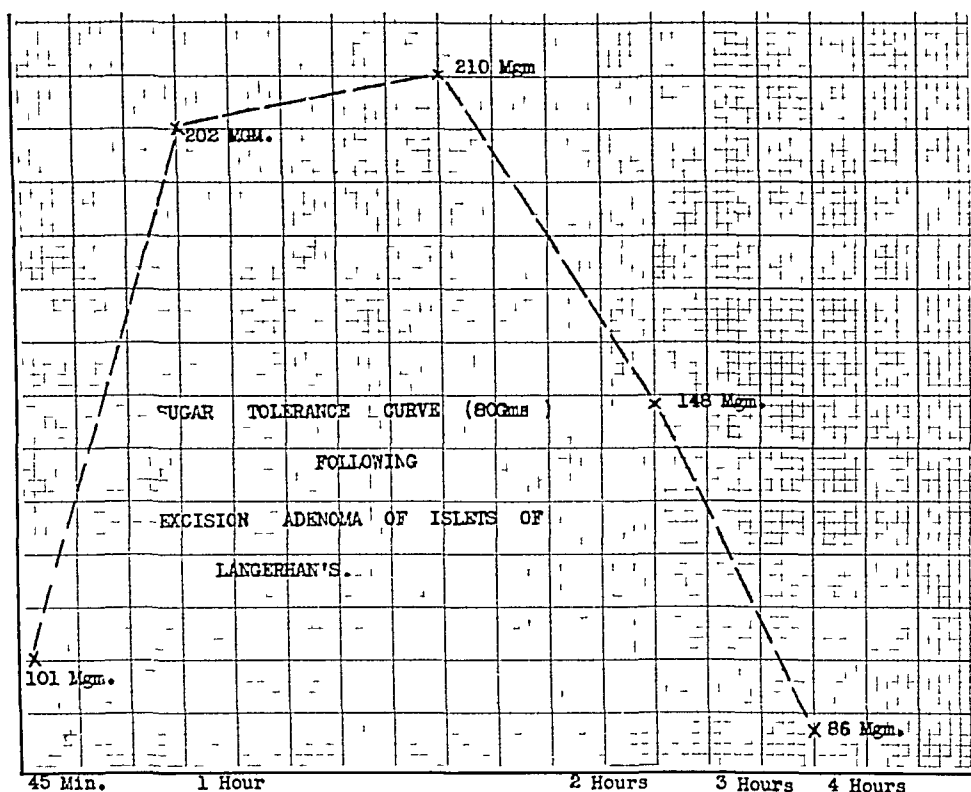


CHART 3

February 6, 1938 Blood sugar 105 mg basal metabolic rate, March 26, 1938,—4
The last blood sugar, determined April 15, 1939, was 90 mg

Relationship of Thyroid to Hypoglycemia—In the approach to the management of this case, it was thought that the episodes of unconsciousness were undoubtedly of hypoglycemic origin. In addition to this the patient appeared to be definitely hyperthyroid both from a clinical and a laboratory standpoint.

In hypoglycemia there is a tendency to an increase in basal metabolic rate. This is thought to be an effort to mobilize liver glycogen and combat the tissue glycopenia. Usually, in hyperthyroid states, then, the tendency has been to a hyperglycemic or diabetic state, in low basal metabolic rate states, such as myxedema, there has been a tendency to hypoglycemia.

The findings in this patient, then, were confusing. With advancing years there is a tendency to hyperactivity in an adenomatous goiter—it being estimated by some observers²² that fully one-quarter to one-third of them become hyperactive later in life. There was nothing to prove or disprove that the thyroid disturbance was secondary to the hypoglycemia. It was felt that operation upon the thyroid was first indicated (1) Because any tendency to a hypoglycemic reaction following the thyroid operation could readily be controlled by administration of intravenous glucose, whereas if the pancreas were first operated upon, there would be much greater difficulty in controlling a hyperthyroid reaction should such occur. (2) It was thought there was some possibility that the patient's extreme emaciation, presumably due to hyperthyroidism, might have so lowered tissue glycogen that a hypoglycemic state resulted. This has been seen¹⁸ on rare occasions in hyperthyroidism.

There was no method of determining whether the patient's hyperthyroidism was independent of the hypoglycemia or whether it was purely a secondary manifestation. If it was a secondary manifestation of the hypoglycemic state, needless to say surgery upon the thyroid was not indicated. Womach and Cole²⁹ have reported a case having signs of exophthalmic goiter with a tendency to hypoglycemia. They first operated upon the pancreas and, although they found no discrete tumor, they did a partial resection of the pancreas with relief of symptoms of hyperthyroidism. They do not advise this procedure in all cases of exophthalmic goiter.

Aitkin² reported a patient having findings typical of exophthalmic goiter, this patient had a thyroidectomy performed. Later, on account of persistency of seizures indicative of hypoglycemia, the pancreas was explored and an adenoma of the islets of Langerhans removed. Since then the patient has developed signs of myxedema and has had to be fed thyroid extract.

However, there have been no cases of adenoma of the islets of Langerhans reported in which hyperthyroidism was associated with an adenomatous goiter.

Diagnosis—No known procedure to definitely prove that a given case of hypoglycemia is due to adenoma of islets of Langerhans has been devised. Whipple²⁵ has established this triad of findings in hypoglycemia as warranting surgical exploration of the pancreas. (1) Definite repeated seizures of a

vasomotor or a psychic disturbance coming on during the fasting period (2) A blood sugar reading below 50 mg per 100 cc (3) Immediate recovery of the seizure with the intake of sugar

Two tests have been used to help establish the diagnosis (1) The insulin tolerance test, and (2) response to adrenalin

In performing the insulin tolerance test five units of insulin are given intravenously after 12 hours of fasting. After two hours there is no tendency for the blood sugar to reach normal if an adenoma of the islets is present. Fraser⁸ used this method to aid in the diagnosis of a case of adenoma of the islets he has recently reported.

John¹⁴ reported the use of insulin in treating three cases of low blood sugar. He administered 20 units t.i.d. p.c. and gave a high fat diet. This differentiates hypoglycemia of functional from hypoglycemia of anatomic origin. If the patient improved with insulin, the low sugar is most likely due to a physiologic disturbance of the islets. The rationale of the treatment is that by giving exogenous insulin the islet cells are put at rest and return ultimately to a normal functional state.

Adrenalin is administered to rule out any disturbance in glycogen reserve. If the blood sugar does not rise after its administration, it would tend to indicate that the hypoglycemic state might be due to lack of liver or tissue glycogen, rather than to a primary disturbance in the pancreas.

Anatomic and Surgical Considerations—Various types of incisions have been advocated in exploring the pancreas (1) The high left rectus which is probably the most common one used, (2) the transverse incision recommended by Whipple,²⁷ and (3) the T-incision used by Finney.⁷

An adequate exposure through a good-sized incision is essential. The pancreas has been most commonly exposed through the gastrocolic omentum, but Judd¹ explored the organ through the gastrohepatic omentum. Whipple²⁶ recommends the use of fine silk ligatures in the pancreas. Tumors have been most frequently found in the region of the body or tail. This is probably due to the fact that the islet cells are most numerous here. The relationship of several important large vessels to the posterior surface of the pancreas must be borne in mind in attacking the organ. These vessels are the aorta, vena cava, the splenic vein and artery, the inferior mesenteric vein, the superior mesenteric artery and vein, and the portal vein. In resecting the pancreas in cases where no tumor was found, Holman¹² recommends splenectomy to adequately control bleeding from the pancreas.

The administration of glucose before, during, and after operation would seem to be a safeguard. It should be administered continuously during operation and for a reasonable period postoperatively. Guerry *et al*¹⁰ have reported a case in which they resected a portion of pancreas and at the conclusion of operation the patient died with a very low blood sugar. They attributed death to "operative insulin crisis." They do not report any post-mortem findings in this case. Only during the first 20 minutes of operation

was 1,000 cc of 10 per cent glucose administered intravenously in the case they report

In examining the pancreas for tumors, a very careful search of the whole gland, both by inspection and palpation, should be made. By incising the peritoneum over the inferior border of the organ, it can be turned up and tumors visualized or palpated more readily. After removing one tumor one should investigate to see if other tumors may be present, as both Whipple²⁷ and Graham⁹ have reported cases with multiple tumors—some of these cases have had only one tumor removed at the original operation and secondary operation has been necessary on account of persistence of symptoms, at which time a second tumor has been disclosed.

Ziskind³⁰ has recently reported a case in which no tumor was noted in the pancreas at operation. A resection of pancreas, together with splenectomy, was then carried out, with the surprising discovery of two adenomata in the resected specimen. There has been a remarkable constancy found in the size of the tumors of the islets, as a rule they are small, being about 1.5 cm in diameter. However, one exceptional case, removed surgically, mentioned by Whipple, weighed 500 Gm.

Pancreatic fistulae have occurred occasionally postoperatively, but have generally been of relatively short duration and produced little difficulty with the wound. Judd¹⁵ mentions one case he had where the fistula persisted for nine months.

General Considerations—The terms hypoglycemia and hyperinsulinism have been used loosely, and by some individuals they have been used interchangeably. This is a gross error. Hypoglycemia is simply a laboratory finding, and there are many causes of such a condition. In marked cases of hypoglycemia, definite symptoms are produced—which symptoms are dependent on the low blood sugar and are the same regardless of what the etiology may be. Appended is a list of the causes of hypoglycemia as given by Judd and Ryneason.¹⁷

(1) Hyperinsulinism

(A) Endogenous—Pancreas

(B) Exogenous—Insulin

(2) Lack of opposing secretions—from disease of suprarenals—tumors of pituitary—any myxedema

(3) Lack of glycogen from liver or wasting muscles—renal diabetic, lactation, and starvation

(4) Interference with regulating center—overactive vagus

Judd¹⁶ has reported two cases, explored for pancreatic islet tumor, in which marked liver damage was found, but no tumors were found in the pancreas. Briggs and Oertling⁷ have reported two cases of extrapancreatic hypoglycemia: one a case of cancer of the stomach with extreme emaciation and an atrophic liver weighing 800 Gm, the second case was one of Addison's disease.

In borderline cases medical management should be carried out for a considerable length of time. Judd¹⁶ emphasized a physiologic disturbance in the islets from vagus effect, resulting in low blood sugars, and advised against resection in such cases. McCaughan and Brown²⁰ reported seven cases where they had resected relatively large portions of pancreas in borderline hypoglycemic states without satisfactory results. (Such a procedure could be likened to gastro-enterostomy for hyperacidity without demonstrable pathology in the stomach or duodenum. Such gastro-enterostomies never gave relief of symptoms and often created a worse state of affairs than already existed.)

Where operation fails to disclose any gross disturbance in the pancreas, further search of the abdomen should be made before resection of the pancreas. Possible sources of islet adenomata, other than in normal pancreas, are in accessory pancreatic rests or in pancreatic tissue in Meckel's diverticulum or dermoid cysts of the ovary of the female.

The sugar tolerance curve following operation in the case herewith resembles a diabetic curve now. It is altogether conceivable that the patient has a pancreatitis with disturbance in her remaining islet tissue and is a mild diabetic. This would fit in well with the fact that both cholelithiasis and hepatitis were found at operation.

SUMMARY AND CONCLUSIONS

(1) A case has been reported in which hyperfunction existed in both an adenomatous goiter and in an adenoma of the islets of Langerhans, these two conditions were corrected by appropriate surgical therapy.

(2) Biologic assays of the tumor tissue removed from the pancreas definitely proved its insulin activity.

(3) The most important clinical feature of hyperinsulinism is that the attacks of coma or unconsciousness come on when the patient has abstained from food for some time or has exercised, the coma-like episodes are relieved spectacularly by administering sugar.

(4) The importance of blood chemistry in states of unconsciousness, coma, or where there is any mental disturbance of questionable origin cannot be overemphasized.

(5) It is important to differentiate hypoglycemia from hyperinsulinism.

(6) The pancreas should be attacked surgically only in those cases where it seems definitely the source of trouble. It should be realized that there are functional hypoglycemic states where operation is definitely contraindicated.

(7) Where an adenoma or adenomata has been found at operation the results have been spectacular, much more so than in cases where no tumor was found and a resection of the pancreas was carried out.

(8) In doubtful cases, surgical intervention directed to the pancreas is justifiable when other causes of hypoglycemia have been ruled out, bearing in mind that undue procrastination may permit an operable malignant lesion of the islets to become inoperable.

REFERENCES

- ¹ Allan, Frank N, Boeck, William C, and Judd, E Starr Surgical Treatment of Hyperinsulinism Col Papers of Mayo Clin, and Mayo Found, 21, 470-476, 1929
- ² Attkin, Louis F Diagnosis and Treatment of Hyperinsulinism Med Clin North Amer, 20, 393-410, 1936
- ³ Banting, F C, and Best, C H Internal Secretion of Pancreas Jour Lab and Clin Med, 7, 251, February, 1922
- ⁴ Best, C H, Jephcott, C M, and Scott, D A Insulin in Tissues Other Than the Pancreas Amer Jour Physiol, 100, 285, 1932
- ⁵ Briggs, John Francis, and Oerting, Harry Extrapaneatic Hypoglycemia Amer Jour Dis and Nutrit, 3, 1936-1937
- ⁶ Cowley, T London Med Jour, 9, 286, 1788
- ⁷ Finney, J M J, and Finney, J M J, Jr Resection of the Pancreas Tr Am Surg Assn, 46, 268, 1928, ANNALS OF SURGERY, 88, 584-592, 1928
- ⁸ Fraser, Russell, Maclay, W S, and Mann, S A Hyperinsulinism Due to Pancreatic Islet Adenoma Quat Jour Med (New Series), 7, No 25, January, 1938
- ⁹ Graham, E A, and Hartmann, A F Subtotal Resection of the Pancreas for Hypoglycemia State Due to Islet Tumors of the Pancreas and Other Conditions Surg, Gynec and Obstet, 56, 728-742, 1933
- ¹⁰ Guerry, Le Grand, and McCutcheon, George T Operative Insulin Crisis in Resection of the Pancreas ANNALS OF SURGERY, 104, 662-665, 1936
- ¹¹ Harris, S Hyperinsulinism and Dysinsulinism J A M A, 83, 729, September, 1924
- ¹² Holman, E, and Railsback, O C Partial Pancreatectomy in Chronic Spontaneous Hypoglycemia Surg, Gynec and Obstet, 56, 591, March, 1933
- ¹³ Howland, G, Campbell, W R, Malby, E J, and Robinson, W L Dysinsulinism, Convulsions and Coma Due to Islet Cell Tumor of Pancreas with Operation and Cure J A M A, 93, 674, August 31, 1929
- ¹⁴ John, Henry J Further Observations on the Treatment of Hyperinsulinism with Insulin Endocrinology, 19, 1935
- ¹⁵ Judd, E Starr, Allen, Frank N, and Ryneerson, Edward H Hyperinsulinism—Its Surgical Treatment Col Papers of Mayo Clin and Mayo Found, 25, 131-138, 1933
- ¹⁶ Judd, E Starr, Kepler, Edwin J, and Ryneerson, Edward H Spontaneous Hypoglycemia Report of Two Cases Associated with Fatty Metamorphosis of the Liver Col Papers of Mayo Clin, and Mayo Found, 25, 105-113, 1933
- ¹⁷ Judd, E Starr, and Ryneerson, Edward H Hypoglycemia Col Papers of Mayo Clin, and Mayo Found, 27, 537-541, 1935
- ¹⁸ Kepler, E J Personal communication
- ¹⁹ Langerhans, P Beitrage zur Mikroskopischen Anatomie der Bauchspeicheldruse Inaug Diss, Berlin, Lange, 1869
- ²⁰ McCaughan, John M, and Brown, Gowen The Value of Partial Pancreatectomy in Convulsive States Associated with Hypoglycemia ANNALS OF SURGERY, 105, 354-369, 1937
- ²¹ Schulze, W Die Bedeutung der Langerhans'-schen Inseln im Pankreas Arch f Miks Anat u Entwickl, 56, 491, 1900
- ²² Sistrunk, W E The Indications for Surgical Treatment in Various Types of Gorter Col Papers of Mayo Clin, and Mayo Found, 12, 330-336, 1920
- ²³ Ssobolew, J W Uber die Structure der Bauchspeicheldruse unter gewissen pathologischen Bedingungen Zentralbl f Allg Path u path Anat, 11, 202, 1900
- ²⁴ Whipple, Allen O Personal communication
- ²⁵ Whipple, Allen O The Surgical Therapy of Hyperinsulinism Jour Internat Chir, 111, No 3, May-June, 1938
- ²⁶ Whipple, Allen O Hyperinsulinism Nelson's Loose Leaf Surgery, Reprint, 1935

- ²⁷ Whipple, Allen O, and Frantz, Virginia F Adenoma of Islet Cells with Hyperinsulinism ANNALS OF SURGERY, 101, 1299, June, 1935
- ²⁸ Wilder, R M, Allen, R N, Power, M H, and Robertson, H E Carcinoma of Islands of Pancreas, Hyperinsulinism and Hypoglycemia J A M A, 89, 348, July 30, 1937
- ²⁹ Womach, Nathan A, and Cole, Warren H The Thyroid Gland in Hypoglycemia ANNALS OF SURGERY, 105, 370-378, 1937
- ³⁰ Ziskind, Eugene, and Bayley, Walter A Hyperinsulinism Jour Lab and Clin Med, 23, 231-240, December, 1937

CONGENITAL HEMOLYTIC JAUNDICE

REPORT OF A CASE WITH NORMAL FRAGILITY AND NORMAL RETICULOCYTE
COUNT, CURED BY SPLENECTOMY

ANSON G HURLEY, M D ,

AND

WILL C MOORE, M D

MUNCIE, IND

A HEMOLYTIC type of jaundice is only occasionally encountered in a surgical practice. Of these the majority occur as the result of acute blood destruction from infections or toxins. Nevertheless, a knowledge of the conditions which are known as congenital and acquired hemolytic jaundice is essential because of the frequency with which they must be considered in the differential diagnosis of diseases of the liver, gallbladder and spleen.

Minkowski,¹ in 1900, emphasized the hereditary character of the congenital type and gave an accurate description of the clinical features of the disease. Chaufford,² in 1907, demonstrated the increased fragility of the red cells. Naegeli³ first stressed the importance of the increased spherocytosis of the red cells. This finding has been noted and confirmed by other observers⁴ (Vaughan and Goddard, 1934, Hayden, 1934, Hawksley and Baily, 1934, Paxton, 1935, Thompson, 1936). Hayden⁵ is of the opinion that the anemia, jaundice, splenomegaly, reticulocytosis and increased fragility are all secondary to the globular form of the erythrocyte. Hayden found decreased cell diameter and increased volume-thickness in all of 12 cases examined. The mean corpuscular volume was variable. It appears likely that microcytosis is a characteristic feature of the disease. However, due to the increased thickness of the cells, mean corpuscular volume may be increased to above normal.

Thompson,⁶ from the examination of the spleens from 30 cases presenting the clinical symptoms of hemolytic jaundice, came to the conclusion that hemolytic jaundice is a definite clinical and pathologic entity. He further stated that the reticulocytes are markedly increased in all instances, ranging from 15 to 50 per cent. He also stated that the majority of red cells are microcytes and the presence of microcytosis is necessary for the diagnosis. In all of his cases he reported that there was an alteration in the fragility of the red cells, which persisted together with microcytosis after splenectomy. In 1936, Thompson⁷ reported his series of cases, which had increased to 45, and his conclusions were basically the same as in his article which appeared in 1932.⁶

Medical teaching and writing have led clinicians to expect to find an increase in the fragility of the red cells and an increased number of reticulocytes in the circulating blood in cases of congenital or acquired hemolytic jaundice.

Submitted for publication June 9, 1939

Chaufford,² in 1907, was the first to recognize an increase of the reticulocytes in the circulating blood as a feature of chronic congenital and acquired hemolytic jaundice. Reticulocyte counts of over 20 per cent have been reported by many authors. Vaughan⁹ reports 35 cases in which reticulocyte counts were made. It was increased in 32 cases, the maximum count being 60 per cent. The count was normal in three cases. No correlation was found between the reticulocytosis and the degree of the anemia.

Gansslen¹⁰ states that 10 per cent of the cases do not show the typical abnormality of increased fragility of the red cells. Bockus and Tumen¹¹ state that microcytosis and increased fragility are the most constant features of the disease, but that the fragility is normal in about 10 per cent of the cases. They point out that in no other disease is such a high percentage of reticulocytes present.

Baty¹² reports a case in which 92 per cent of the red cells were found to contain reticular material and occasional cells with nuclei and nuclear bodies were seen. Two years after the removal of the spleen the patient showed reticulocyte counts of 30–70 per cent and signs of continued activity of the disease. Reynolds¹³ reports a case of acquired hemolytic jaundice in a 21-year-old male, who was well until 17 months before admission, in whom the fragility of the red cells was only slightly altered and reticular material was present in 95 per cent of the red cells. This patient was cured by splenectomy, and the fragility test over three years following splenectomy was normal.

Some investigators believe that immature red blood cells, at least in certain disorders of the blood, are more resistant to hemolysis by hypotonic sodium chloride solution than are the adult cells, while others hold that this is not the case.

There are in the literature cases of unquestionable chronic congenital or acquired hemolytic jaundice with normal fragility tests and normal reticulocyte counts which were cured by splenectomy. Such a case is presented herewith, because of its several features which are at variance with the usual case of chronic, congenital hemolytic jaundice and because of its very rapid and dramatic cure following splenectomy.

Case Report—Hosp. No. 31,481. H. M., white, male, age 33, was admitted to the Ball Memorial Hospital, September 11, 1934, complaining of vomiting, weakness, jaundice, pain in the right upper quadrant, and loss of weight.

Onset and Course—The patient stated that he had been yellow, *i e.*, jaundiced, off and on all his life. His condition was noticed three days after he was born and had continued to be present ever since. However, there were times when the jaundice was mild and other times when it was quite deep. It did not seem to interfere with his health in any great degree, he was able to work and to carry on a fairly normal life until the onset of his present complaints, which developed on month ago. At that time he had a very severe headache which was relieved after three days, and patient thinks that the jaundice probably deepened at this time. After the headaches were relieved, the patient started to vomit and he was unable to keep food on his stomach for ten days but vomited water only twice during that period. During this time he had pains in his abdomen (R.U.Q.) off and on. The pains would start in the right flank and radiate medially along the line of the lower right ribs to the midepigastria region. One

attack of this pain was definitely colicky in nature, very severe and he vomited considerably. Afterwards he was somewhat relieved. The bad attack occurred about 11 days previous to admission, since which episode he has been improving, he has not vomited since, has had a fairly good appetite, has had but a small amount of pain in the right upper quadrant and, in general, has felt pretty well except for weakness. At present, he is jaundiced but not having any pain, is not nauseated, and tolerates food.

He had lost about 30 pounds during the last month. Varying degrees of jaundice had been present since birth but he had not had itching of the skin. Headaches were rare. Severe one at onset of present illness. Tinnitus and dizziness only when attempting to get up since beginning of present trouble. There had been no cough or hemoptysis. Some dyspnea on exertion. Says he has had heart trouble since 1918 following an attack of "flu." Occasionally ankles swell. No precordial pains. His appetite had been good until onset of present complaint and for the last ten days. Had no trouble in eating fatty foods before onset of complaint. Dyspepsia is caused by cucumbers and unripe bananas. Did not have clay-colored stools during present trouble and there is no history of them having been noticed previously. Has not been constipated. There has been no burning or frequency of urination. Urine is usually fairly yellow, but the color has varied from time to time. No hematuria. Seems to think he passes a normal amount of urine.

The patient does not know about childhood diseases except he recalls having had the mumps. No scarlet fever, no typhoid fever, no pneumonia. Has enjoyed fairly good health.

Family History—Father, age 58, living and well. Has never been jaundiced. His parents were never jaundiced. Mother died at age of 40, and was never jaundiced. Her parents were never jaundiced. Two brothers living and well. Two sisters and one brother died in infancy. Patient does not know the cause of their death.

Physical Examination—The patient is a well nourished and well developed white male with a marked icteric tint to skin and sclerae. Is not in pain but appears to be moderately chronically ill. T 99° F, P 90, R 20, B P 128/35. No falling of hair, no gross abnormalities of the head. The eyes react to light and accommodations and their movements are normal. The tongue is somewhat dry, cryptic tonsils, no pharyngeal infection. The thyroid is smooth and small, no cervical adenopathy. The chest shows equal expansion. The lung resonance seems slightly impaired posteriorly, normal vesicular breath sounds, no rales. The apex impulse of the heart is visible in sixth left interspace in midclavicular line, no thrills palpable. Slight enlargement to left. None to right. Right border at parasternal line, left at anterior axillary line, 10 cm to left of midsternal line. A systolic murmur is heard at the apex and a faint diastolic at the base over the aortic area. Corrigan pulse. B P 128/35. Pistol shot femorals. Positive Duroziez's sign. The abdomen is not distended, the spleen is easily palpable and is enlarged inferiorly to the level of the umbilicus and mesially to the left paramedian line. The splenic notch is palpable. There is a definite area of tenderness in the right midclavicular line at the costal margin. No rigidity. The extremities are negative. *Clinical impressions* Cholecystitis with cholelithiasis. Old inactive rheumatic heart disease with mitral and aortic regurgitation, possible functional component. Chronic, congenital hemolytic jaundice.

Laboratory Data—Blood, September 11, 1934. Hemoglobin 4.6 Gm, 27.6 per cent, erythrocytes 970,000, poikilocytosis ++, polychromatophilia +, color index 1.4, leukocytes 2,800, eosinophils 0, lymphocytes 20 per cent, neutrophils, band 10 per cent, polys 70 per cent. Urine, September 12, 1934. Clear, acidity low, specific gravity 1.009, albumin negative, sugar faint trace, crystals 0, leukocytes 0, erythrocytes, epithelial 1 plus, granular +, motile bacilli ++++. Blood, September 12, 1934. Van den Bergh, direct reaction and indirect reaction, bilirubin 6.9 mg per 100 cc blood. Icteric index 100,

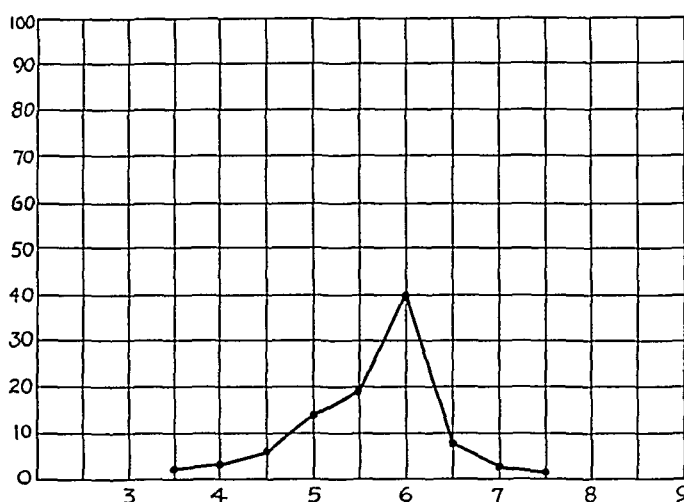
bromsulphalein liver function test normal Fragility test Hemolysis commenced at 0.44 per cent, complete at 0.38 per cent

Price Jones
Erythrocyte Diameter

3 cells at	3.5 microns
4	4.0
6	4.5
14	5.0
19	5.5
40	6.0
8	6.5
4	7.0
2	7.5

Average cell diameter
6 microns

CHART 1—September 16, 1934
Showing the diameter of the erythrocytes



Three days later, September 15, 1934, the patient was given 525 cc of whole blood by the Kimpton-Brown method with no reaction, this was followed in two days by 700 cc with no reaction. The following day 675 cc of blood was given with a subsequent enlargement of the spleen and deepening of the jaundice.

Gastric analysis, September 19, 1934

Specimens	Fasting	15 min	30 min	45 min	60 min
Total acidity	2	2	10	6	18
Free acid	none	none	none	none	none
Quantity (cc)	35	10	8	10	20

No blood found, lactic acid present. Microscopic: Numerous diplostreptococci, many gram-negative and gram-positive bacilli, numerous *Spiriochaeta vincenti*, numerous fusiform bacilli.

Blood, September 21, 1934: Hemoglobin 6.4 Gm, erythrocytes 1,760,000, leukocytes 1,900, eosinophils 1, lymphocytes 48, monocytes 3, neutrophils, band 12, polys 36.

The patient was then given 600 cc of whole blood, September 22, 1934, and 685 cc whole blood, September 24, 1934. On September 25, 1934, the hemoglobin was 9.4 Gm, 64 per cent, erythrocytes 2,170,000. There occurred increasing signs of blood destruction following the transfusions. One cubic centimeter of concentrated liver extract was administered intramuscularly twice a week. He refused to submit to splenectomy and was discharged, September 29, 1934.

Following discharge, the patient received deep roentgenotherapy to the spleen without benefit, and was readmitted, November 8, 1934, for transfusion, at which time he was given 510 cc of whole blood, and the following day was given 675 cc more. The red blood count following these transfusions was 1,910,000, hemoglobin 6.2 Gm, or 37 per cent. He was then discharged but was readmitted, November 20, 1934, at which time he agreed to have splenectomy performed. The red blood count at that time was 1,220,000, hemoglobin 5.4 per cent, and reticulocytes 1.9 per cent. He had approximately 2,200 cc of whole blood administered during the following week.

Operation—Splenectomy was performed, December 1, 1934. The spleen was firmly adhered to the diaphragm, but otherwise the operation presented no technical difficulties. The gallbladder was large and full of small stones. It was not removed or opened. He was given 600 cc of whole blood postoperatively without reaction, and the following day, December 2, 1934, the hemoglobin was 12 Gm, red blood count 3,260,000, reticulocyte

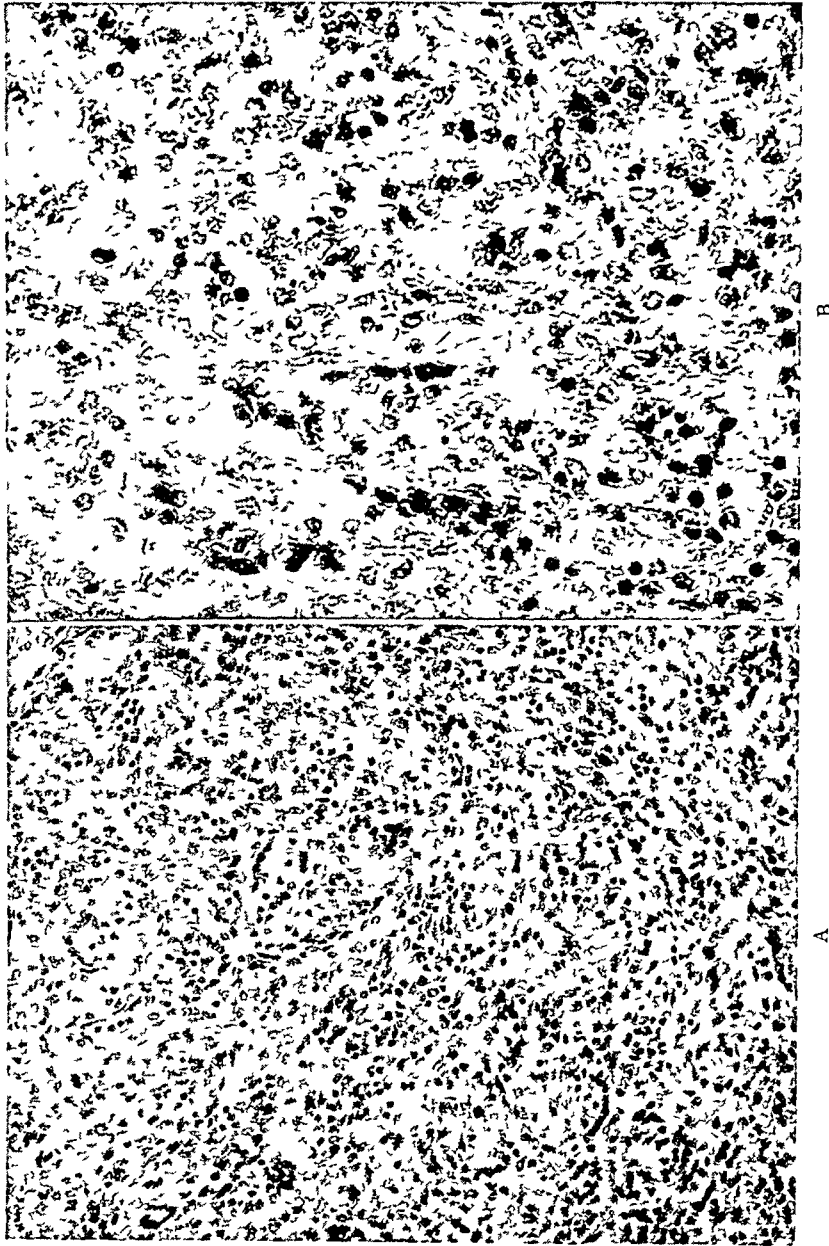
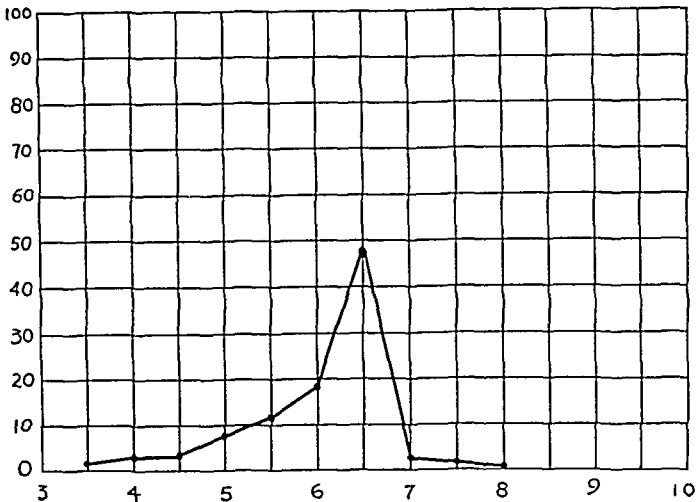


FIG 1—A and B Photomicrographs of the spleen showing striking changes in the splenic sinusoids with the characteristic arrangement of the living cells producing the appearance of pseudo-venous tissue. There is almost complete absence of lymphoid tissue and generalized deposition of pigment (A $\times 240$, B $\times 480$)

count 12.8 per cent, and the leukocytes 20,150, of which 91 per cent were polys. On December 3, 1934, the hemoglobin was 11.8 Gm, red blood count 2,950,000, reticulocytes 11.8 per cent. December 4, 1934, hemoglobin 10.8 Gm, red blood count 2,800,000, reticulocytes 8.4. By this time, which was 48 hours after splenectomy, the jaundice had completely disappeared. Daily blood examinations showed a slow but gradual rise in hemoglobin and red blood count, with a decrease in reticulocyte count to 4.8 per cent on December 12, 1934, and he was discharged in good physical condition, December 19, 1934.

Price Jones	
Erythrocyte Diameter	
2 cells at	3.5 microns
3	4.0
3	4.5
8	5.0
12	5.5
18	6.0
48	6.5
3	7.0
2	7.5
1 cell at	8.0
Average cell diameter	
6.5 microns	

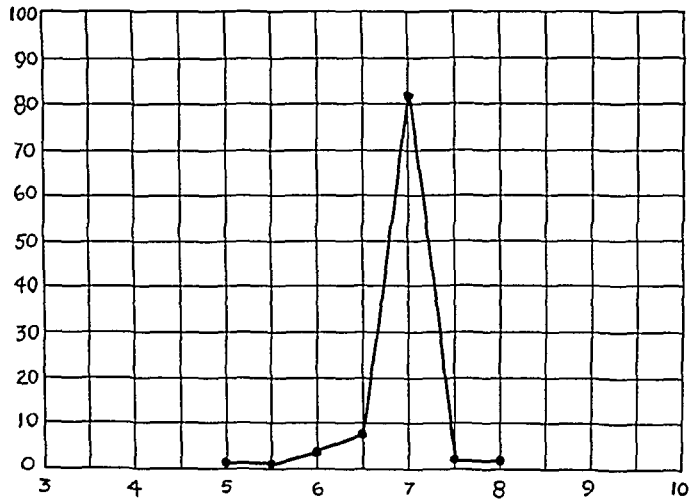
CHART 2—April 2, 1935. Showing the diameter of the erythrocytes



Pathologic Examination—Gross. Dr. Lall G. Montgomery. The spleen weighed 1,577 Gm and measured 24 x 17 x 6 cm. There is perisplenitis Grade II, especially marked over the diaphragmatic areas, where there is an adhesion to the diaphragm measuring

Price Jones	
Erythrocyte Diameter	
1 cell at	5.0 microns
1	5.5
4 cells at	6.0
8	6.5
82	7.0
2	7.5
2	8.0
Average cell diameter	
7 microns	

CHART 3—October 11, 1939. Showing the diameter of the erythrocytes



5.5 x 3.5 cm. *Microscopically*, the splenic capsule is slightly thickened and there are scattered foci of chronic capsulitis. There are also scattered fibrous adhesions arising from the capsule. There is almost complete absence of lymphoid tissue except around occasional trabeculae. The pulp is occupied by great numbers of erythrocytes, and scattered widely throughout the sections are large amounts of brownish pigment. The most striking feature of this section is the appearance of the splenic sinuses, the lining cells of which present the characteristic arrangement so often found in the spleen of hemolytic jaundice, which gives them the appearance of being arranged in pseudo-acini (Fig. 1 A and B). This appearance is seen throughout the section. *Pathologic Diagnosis*. Typical of the spleen found in cases with hemolytic jaundice.

Subsequent Course—Within one month following the patient's discharge from the hospital he returned to work as a garage mechanic. On April 2, 1935, his blood count showed Hemoglobin 16.8 Gm, 100.8 per cent, erythrocytes 4,750,000, leukocytes 7,550, no reticulocytes. Hemolysis began at 0.42 and was complete at 0.34. On April 1, 1939, hemoglobin 13.5 Gm, 81 per cent, color index 1.1, erythrocytes 3,630,000, an occasional monoblast was present, leukocytes 6,900. Fragility began at 0.45 and was complete at 0.35. Volume index 1.1.

The patient has not had gallbladder symptoms subsequent to his first admission to the hospital. Oral cholecystography, April 12, 1939, revealed a small, functioning gallbladder, with the shadow of one stone, about 0.8 cm. in diameter, in the fundus.

COMMENT—During the period of observation of this case microcytosis has not been observed. The critical condition of the patient so strongly indicated repeated transfusions that only two days' observation prior to transfusion was possible.

In the presence of severe anemia and an absence of microcytosis the findings of a normal fragility of the circulating red cells seems plausible. An interesting association between microcytosis and increased fragility is brought out by the observation of Krumbhaar¹⁴ that in various mammals those with the smaller red cells have the higher fragility.

Dawson¹⁵ reports that five of 40 collected cases showed normal fragility of the red cells. Buch and Jaffe¹⁶ report two cases of hemolytic jaundice occurring in adolescence with normal fragility of the red cells and normal reticulocyte counts. Both cases were cured by splenectomy.

Some authors (Cheney and Cheney,¹⁷ and Reynolds¹⁸) have attempted to explain normal fragility on the basis that reticulated red cells are more resistant to hemolysis than normal red cells. While it may be true that reticulated red cells are more resistant than normal, their hypothesis will not explain the normal fragility encountered in the cases of Buch and Jaffe¹⁶ and in the author's case.

It is interesting to note that in the case reported by Reynolds¹⁸ the fragility test was normal, partial hemolysis beginning at 0.4 per cent sodium chloride solution and complete hemolysis at 0.32 per cent. At that time, 95 per cent of the cells showed reticular material.

The cases reported by Baty¹² showed concomitant increased fragility and high reticulocytosis (92 per cent). It appears from a review of the literature that the occurrence of reticular material in the red cells is not the factor responsible for normal fragility when it is encountered.

In the author's case, partial hemolysis of transfused blood was occurring before splenectomy. This was manifested clinically by the increase in the size of the spleen following transfusions, mild reactions, deepening of the jaundice and inability to effect any prolonged increase in the red cell count with frequent large transfusions.

If the spleen becomes overactive in blood destruction function and will destroy normal transfused red cells, it seems plausible to believe that it would rapidly destroy the less resistant red cells as they come into the blood stream and leave circulating the more resistant cells.

Gallstones occur in about 60 per cent of the patients with congenital or acquired hemolytic jaundice. The stones are usually composed almost entirely of the pigment which is present in the bile in great excess. Brooks¹⁸ reports a case of congenital icterus with gallstones in a patient four years old, in whom the spleen was removed and the gallbladder drained. In the author's case there has been, apparently, an almost complete disappearance of the gallstones following splenectomy, as far as is evidenced in the roentgenogram.

In view of the pathologic physiology in these cases with gallstones, it appears rational that biliary tract operations should be reserved for cases of obstruction of the common, hepatic or cystic ducts.

REFERENCES

- ¹ Minkowski, O. *Verhandl. D. Deutsch. Kongr. f. inn. Med.*, **18**, 316, 1900.
- ² Chauffard, A. *Semaine Med.*, **27**, 25, 1907.
- ³ Naegeli, O. *Blutkrankheiten und Blutdiagnostik*, 5th ed., Berlin, Julius Springer, p. 292, 1931.
- ⁴ Vaughan, J. M., and Goddard, H. M. *Lancet*, **1**, 513, 1934.
Hayden, R. L. *Am. Jour. Med. Sci.*, **188**, 441, 1934.
Hawksley, J. C., and Bailey, W. M. *Lancet*, **2**, 1329, 1934.
Paxton, W. T. W. *Arch. Dis. Child.*, **10**, 421, 1935.
Thompson, W. P. *J. A. M. A.*, **107**, 1776, 1936.
- ⁵ Hayden, R. L. *Am. Jour. Med. Sci.*, **188**, 441, 1934.
- ⁶ Thompson, W. P. *Johns Hopkins Hosp. Bull.*, **365**, 1932.
- ⁷ Thompson, W. P. *J. A. M. A.*, **107**, 1776, 1936.
- ⁸ Meulengracht, E. *Der chronische hereditäre, hämolytische Icterus*. Leipzig, Klinkhardt, p. 19, 1922.
- ⁹ Vaughan, J. M. *Jour. Path. and Bact.*, **45**, 56, 1937.
- ¹⁰ Gannslen, M., Zipperlen, E., and Schuz, E. *Deutsch. Arch. f. klin. Med.*, **146**, 2, January, 1925.
- ¹¹ Bockus, H., and Tumen, H. *Cyclopedia of Medicine*. F. A. Davis Co., **7**, 598, 1933.
- ¹² Baty, J. M. *Am. Jour. Med. Sci.*, **179**, 546, 1930.
- ¹³ Reynolds, G. P. *Am. Jour. Med. Sci.*, **179**, 549, 1930.
- ¹⁴ Krumbhaar, E. B. *Cowdry's Spinal Cytology*, New York, Hoeber, 285, 1928.
- ¹⁵ Dawson, B. E. *Brit. Med. Jour.*, **1**, 921-928, May 30, 1931.
- ¹⁶ Birch, C. L., and Jaffe, R. H. *Med. Clin. North Amer.*, **12**, 255, July, 1928.
- ¹⁷ Cheney, W. F., and Cheney, G. *Am. Jour. Med. Sci.*, **187**, 191, 1934.
- ¹⁸ Brooks, C. D. *Am. Jour. Surg.*, **29**, 319, August, 1935.

ACUTE CHOLECYSTITIS PRECEDING NEOPLASTIC COMMON BILE DUCT OBSTRUCTION

ROBERT E. ROTHENBERG, M.D.

AND

SHEPARD GERARD ARONSON, M.D.

BROOKLYN, N. Y.

FROM THE SURGICAL SERVICES OF THE JEWISH HOSPITAL, BROOKLYN, N. Y.

THE PURPOSE of this communication is to report a series of eight cases in which acute cholecystitis occurred during the early course of neoplastic common bile duct obstruction. The cases are interesting in that one can trace the origin of the acute exacerbation of the cholecystitis and can appreciate the factors which led to its development. Also, the cases are of surgical importance in that the underlying malignant lesion was overlooked in every instance because of the acuteness of the gallbladder inflammation.

The patients, consisting of six females and two males, were admitted to the hospital and operated upon because they presented symptoms and signs suggestive of an acute lesion in the biliary tract. All of the patients complained of upper abdominal pain, and in addition, six of them gave a history of belching, pyrosis, and aversion for fatty foods. Similar attacks, dating from one to 25 years prior to hospital admission, had occurred previously in six of the cases. In seven of the patients, the type of pain was characteristic of biliary colic, whereas the eighth patient complained of severe left upper quadrant abdominal pain with radiation to the upper right quadrant and to the back. On admission, the temperature was moderately elevated in all but two cases. The two patients with normal temperature had been suffering from their acute cholecystitis for two weeks and one month prior to hospitalization. Physical examination revealed muscle spasm and tenderness in the right upper quadrant of the abdomen in every instance. Three patients presented tender, palpable gallbladders, but no other abdominal masses were found.

None of the patients had noted jaundice in their previous attacks of cholecystitis, although three of them were definitely icteric on admission. Of the jaundiced patients, two were suffering from their first attack of gallbladder disease. The third had had repeated episodes of pain for ten months but had been jaundiced for only ten days prior to hospitalization.

The preoperative diagnosis in six cases was acute cholecystitis. The other two patients were thought to have obstructive jaundice due to stone or to a carcinoma pressing upon the common bile duct. The operative findings, however, did not seem to substantiate the clinical impression of malignancy in either of these latter two cases. At operation, gangrenous cho-

lecystitis was found in two cases, empyema of the gallbladder in one case, and acute inflammatory cholecystitis in the other five. Cystic duct calculi were encountered in five cases. The other three patients had acute non-calculous cholecystitis.

The operative notes in four cases stated that the common duct and head of the pancreas were free from pathology. In one case, where the omentum was wrapped around a perforating gangrenous gallbladder, no mention was made of the pancreas or common bile duct. One surgeon noted that the pancreatic head was "somewhat enlarged but not the seat of malignancy," and another surgeon found the pancreas to be "soft and edematous." Common bile duct compression by three enlarged lymph nodes was stated as an auxiliary finding in the eighth case. In no instance did the operator suspect that he was dealing with anything but an acute cholecystitis. More complete reports on operative findings will be found in the abstracts of the case records.

Cholecystectomy was performed upon six patients and cholecystostomy upon the other two. A small section of the gallbladder wall was removed from both patients on whom cholecystostomy had been performed. Unfortunately, the microscopic section of the gallbladder of one case could not be located. However, the operating surgeon described the specimen as follows: "Gangrenous gallbladder wall containing frank pus and a few stones." Examination of the microscopic sections in the other seven cases revealed an acute cholecystitis, in most instances superimposed upon chronic inflammation. None of the gallbladders showed any neoplastic tissue. The pathologic reports are given in detail in the abstracts of the case records, and photomicrographs of sections of the gallbladder wall will be found elsewhere in this report.

Seven of the eight patients recovered from the gallbladder operation, although convalescence was complicated in four instances. It is interesting to note that the operative findings in the three patients who had the most uneventful postoperative courses stated that the pancreas and common duct were normal. Evidently the compression of the common bile duct by the growing neoplasm was not yet great enough to retard operative recovery. A right hemiplegia developed in one patient on the tenth postoperative day, but the course was otherwise uncomplicated and the patient eventually became well enough to be discharged from the hospital. One patient, upon whom cholecystostomy had been performed, failed to drain sufficient bile, probably because the acute inflammation had caused a temporary blocking of the cystic duct. She was able to leave the hospital after 15 days of postoperative convalescence, but still showed a moderate icterus and inadequate biliary drainage. Two patients who had been subjected to cholecystectomy ran a markedly febrile course but managed to attain operative recovery after developing biliary fistulae. The eighth patient died three days following cholecystostomy for an empyema of the gallbladder. In this case, the underlying malignant lesion was unexpectedly discovered at autopsy.

The histories of the interval course, from the time of hospital discharge to readmission, bore great similarities. Weakness, anorexia and weight loss occurred in all cases. No patient made a sufficiently complete recovery so that he or she could return to the performance of normal duties. Case 1 developed jaundice a few days after discharge from the hospital and continued with symptoms of biliary disease for the 13½ weeks between hospitalizations. Case 2 became jaundiced ten weeks following discharge from the hospital and was readmitted in the middle of the thirteenth week. Case 3 continued to have abdominal pain and other preoperative symptoms for the entire interval of 11 weeks, from the time of the first discharge to second admission to the hospital. Case 4 also failed to have symptomatic relief following the gallbladder operation and was readmitted to the hospital ten weeks later. Case 5 showed progressive weight loss, anorexia, and weakness during her interval period. The biliary fistula continued to drain, but icterus continued and the patient was forced to seek readmission to the hospital 24 weeks after her first discharge. Case 6 came back to the hospital two weeks following her discharge. She had had chills, fever, and abdominal pain throughout the entire interval. Case 7 developed a postoperative biliary fistula and maintained a fair state of health for the first 12 weeks after leaving the hospital. He then developed jaundice which receded spontaneously after two weeks. Readmission to the hospital, 20 weeks after his first discharge, was necessitated by a second recurrence of jaundice. (As previously mentioned, Case 8 died three days following first operation.) In six of the above seven cases, the appearance of jaundice was the deciding factor which led to readmission to the hospital. The nonicteric patient was readmitted with a diagnosis of subhepatic abscess.

On second admission, all of the patients looked chronically ill. There were none of the acute findings of abdominal tenderness and muscle spasm which had been present on previous examination. An abdominal mass in the region of the scar of the gallbladder operation could be palpated in three of the seven cases. The clinical impression in six cases was common bile duct obstruction. Carcinoma of the head of the pancreas or bile ducts was considered as the cause of obstruction in five of these cases, although common duct stone or common duct stricture was also mentioned as a possible diagnosis. The sixth case was thought to have a calculus which had been overlooked at the previous operation, and the seventh patient was diagnosed preoperatively as having a subhepatic abscess.

A markedly enlarged, firm, nodular head of the pancreas was found at operation in four cases. A mass arising from the region of the common bile duct was discovered in two cases. The underlying malignant lesion was found in the two remaining cases at autopsy. The pathologic specimens of malignancy were obtained by biopsy at operation in four cases, whereas, three other specimens were obtained only at autopsy. Thus, there is but one case in which no microscopic section is available, and in that case, the operating

surgeon stated that the head of the pancreas was markedly enlarged, hard and nodular, with enlargement extending up along the common duct

The three pathologic specimens obtained from the common bile duct showed typical carcinoma. The three specimens removed at operation from the head of the pancreas or peripancreatic lymph nodes also showed typical carcinoma. The sections from the seventh patient showed a rhabdomyosarcoma which had originated in the upper end of the right iliopsoas muscle and had metastasized widely. Autopsy revealed that the head of the pancreas was infiltrated with metastatic tissue and was surrounded by large, pale-gray and pale-yellow lymph nodes which, microscopically, also showed sarcoma. The terminal end of the common bile duct had been constricted by these metastatic nodes. Detailed pathologic reports as well as photomicrographs of all specimens are to be found with the abstracts of the case records.

ABSTRACTS OF CASE RECORDS

Case 1—Hosp No 73409 S S, white, female, age 52, was admitted to the hospital July 7, 1922, because of excruciating pain in the right hypochondrium, nausea, vomiting and constipation. Pain radiated to right shoulder and around to the back. History of many similar attacks, relieved only by injection of morphine during past 11 years. No jaundice. Physical examination revealed marked tenderness in right upper quadrant of abdomen with a tender, palpable gallbladder. A preoperative diagnosis of acute cholecystitis was made, and the patient was operated upon the day following admission.

Operative Pathology—Gangrenous, distended gallbladder containing a few stones and frank pus. No adhesions to surrounding structures. No other pathology noted.

Procedure—Cholecystectomy.

Patient made an uneventful recovery and was discharged on the eighteenth postoperative day, July 26, 1922.

Within a few days after leaving hospital, the patient began to have pruritus and noticed that her urine was dark in color. Soon thereafter, the family noticed that her skin was "yellow." Two months following discharge from hospital, nausea and vomiting recurred, but no colicky pain. There was steady loss of weight, anorexia, and weakness from the time of gallbladder operation until readmission to the hospital. Patient was readmitted, October 28, 1922, because of the progressive jaundice, weight loss, weakness and vomiting. Physical examination revealed skin to be markedly icteric. Scar in right upper quadrant well healed, no palpable masses. The clinical impression was that the patient was suffering either from constriction of the common bile duct by adhesions, or that a malignancy was present. The second operation was performed, November 3, 1922.

Operative Pathology—Dense adhesions at site of previous cholecystectomy. Very dark cholemic liver. Indurated enlarged pancreas. Induration along common bile duct. Pancreas of stony hardness producing pressure on common bile duct. No calculi palpable.

Procedure—Tissue excised from head of the pancreas and along common bile duct.

Pathologic Examination—The tissue is composed of nests and cords of large cylindric cells varying in size, shape and staining reaction of the nuclei. Many are in mitotic division. In some areas, they form lumina which are widely distended with amorphous, lavender-staining material. In places, tumor tissue is seen within distended endothelial lined spaces. The stroma is abundant, loose and densely infiltrated with small and large mononuclear cells, eosinophils and polymorphonuclear leukocytes. Deposits of calcium are seen at one end of the section. In some areas, too, the lumina are large and are lined by compressed cells. Within such lumina, there are amorphous lavender-staining material and groups of tumor cells (Fig 1). *Pathologic Diagnosis* Adenocarcinoma (colloid).

Postoperatively, the patient did poorly. A biliary fistula developed on the fifth day after operation. The patient was finally discharged from the hospital on the sixtieth post-operative day in poor condition, deeply jaundiced.

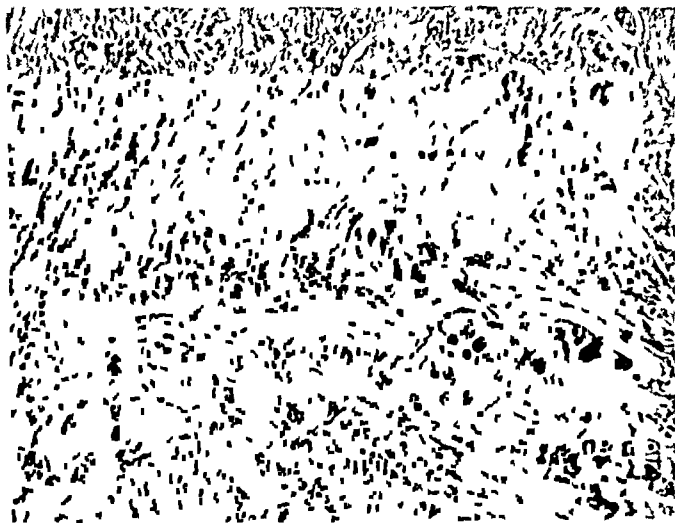


FIG 1—Path No A1088 Photomicrograph showing carcinomatous tissue removed from the head of the pancreas (x250)

Case 2—Hosp No 123590 J B, white, female, age 58, was admitted to the hospital, October 6, 1929, complaining of right upper quadrant abdominal pain for past two weeks. Pain was severe and colicky and caused patient to double up. Nausea, chilly sensations and fever accompanied this attack which recurred several times during the days



FIG 2—Path No 22113 Photomicrograph showing portion of wall of gangrenous gallbladder (x250)

preceding hospitalization. History of abdominal bloating, belching and pyrosis for many years. No jaundice or clay-colored stools. Physical examination showed tenderness and muscle spasm in right upper quadrant of abdomen. Gallbladder was palpable as a tender mass just below the right costal margin. A preoperative diagnosis of an acute exacerbation of a chronic cholecystitis was made.

Operation—Cholecystectomy was performed, October 9, 1929.

Operative Pathology—Gallbladder was three times normal size, full of calculi, con-

taining small amount of pus. Apparent perforation of gallbladder into liver bed. Surrounding liver tissue edematous, boggy, and covered with a plastic exudate. Gallbladder itself embedded in massive adhesions and covered with omentum. Cystic duct edematous and compressed by a large lymph node. Moderate degree of neighboring duodenitis.

Operative Diagnosis Gangrenous cholecystitis

Pathologic Examination—Destruction of the mucosa and necrotic tissue in the wall of the gallbladder which is the seat of areas of polymorphonuclear cell infiltration, edema and extravasation of blood (Fig 2).

Pathologic Diagnosis Acute suppurative cholecystitis with gangrene

Postoperative course was satisfactory until the tenth day when patient suddenly became unconscious and developed paralysis of right arm and right leg. Consciousness eventually returned and patient was found to have a motor aphasia. The abdominal wound healed and patient was discharged from hospital on the thirty-fifth day after operation.

Subsequent Course—Ten weeks following hospital discharge, pruritus and jaundice appeared. On readmission, February 9, 1930, the patient was found to be deeply jaundiced and to have acholic stools. No abdominal pain during interval between hospital discharge and readmission. Except for the residual signs of the hemiplegia and the deep jaundice, physical examination revealed no significant findings. Abdomen was soft and flat, no masses palpable.

Preoperative Diagnosis Common duct obstruction, due either to stricture secondary to previous cholecystectomy or to malignancy. The second operation took place ten days following readmission, February 19, 1930.

Operative Pathology—No free fluid in peritoneal cavity. Liver slightly enlarged, congested, showing evidence of biliary cirrhosis. Duodenum and pylorus firmly adherent to liver in region of portal fissure. A marked cartilaginous cicatrix at the upper part of the common duct just below the junction of the cystic duct was found. No evidence of suppuration. Head of pancreas moderately enlarged, but no evidence of neoplastic pathology.

Procedure—Adhesions between liver, pylorus, duodenum and common duct separated. A portion of tissue which was involved in the cicatrix about the common duct was excised, thus releasing some of the constriction on the common duct. Rubber dam inserted in Morrison's pouch.

Pathologic Examination—Specimen is an ovoid mass of tissue 4 cm in diameter. Examination shows tissue to be made up of carcinomatous masses, the cells of which appear to be highly malignant (Fig 3).

Postoperatively, the patient did very poorly, despite intermittent drainage of bile through the abdominal wound. Cholemia became marked. Patient was discharged from hospital, deeply jaundiced, in poor condition, on the forty-eighth day following operation.

Case 3—Hosp No 184215. N. M., white, female, age 47, was admitted to the hospital, October 1, 1935, because of very severe recurrent epigastric pain, epigastric distress, belching, anorexia and weight loss of one year's duration. Pain much worse during the five months previous to admission. The epigastric pain radiated to the back. Roentgenograms, taken prior to admission, revealed calculi in the gallbladder.

Physical Examination—Spasticity and tenderness in the right upper quadrant, no masses palpable. No jaundice. A preoperative diagnosis of subacute cholecystitis and cholelithiasis (acute exacerbation of chronic cholecystitis) was made and the patient operated upon on the third hospital day.

Operative Pathology—Acutely inflamed, distended gallbladder, opaque, about three times normal size, with moderately thickened walls. Numerous adhesions between gallbladder and surrounding structures. A large stone was impacted at the junction of the ampulla and cystic duct. No pathology noted along the common duct, in the pancreas or duodenum.

Procedure—Cholecystectomy

Pathologic Examination—The mucosal coat is markedly hypertrophied. There is an increase of the intermuscular and perimuscular connective tissue. All the layers are somewhat edematous and in areas show freshly extravasated blood. An infiltration

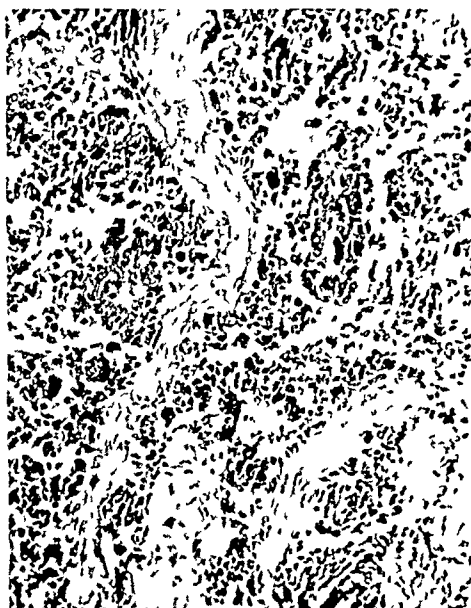


FIG 3—Path No 23285 Photomicrograph showing carcinoma of the common bile duct ($\times 250$)



FIG 4—Path No 982 Photomicrograph showing a portion of the gallbladder wall involved in an acute inflammatory process ($\times 180$)

of polymorphonuclear leukocytes and large mononuclear cells is seen in the tunica propria, in the intermuscular connective tissue and the perimuscular connective tissue (Fig 4).
Pathologic Diagnosis Acute and chronic cholecystitis

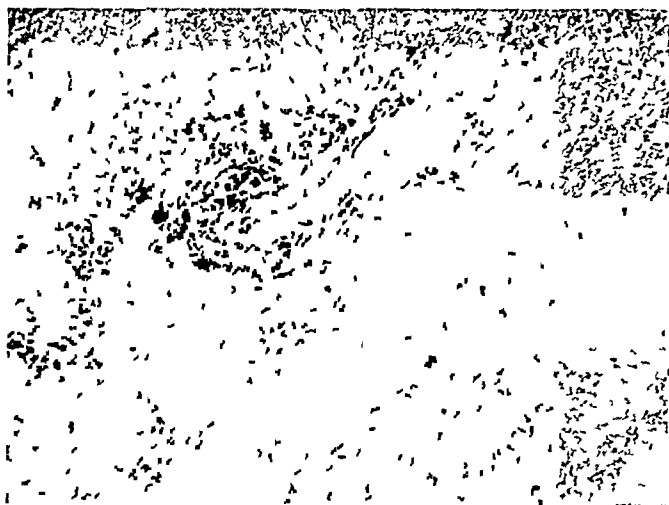


FIG 5—Path No 2112 Photomicrograph showing peripancreatic lymph node with metastatic carcinoma ($\times 170$)

Patient made an uneventful recovery and was discharged on the seventeenth post-operative day, October 19, 1935.

Subsequent Course—Immediately upon leaving the hospital, the patient experienced recurrent pains of the same nature as those experienced previous to operation. Loss of

weight continued and patient vomited occasionally. Patient was readmitted, January 2, 1936, three months after being discharged, with continuous severe epigastric pain radiating to the back. Physical examination revealed a markedly emaciated woman, jaundiced. Scar of previous operation well healed, with a mass the size of an egg running from its upper one-third toward the midline. Clinical impression was a carcinoma of the head of the pancreas. Patient was reoperated upon, January 4, 1936.

Operative Pathology—A hard, nodular mass about the size of a small grapefruit, involving the entire pancreas from head to tail.

Procedure—A small, hard node situated over the head of the pancreas was taken for biopsy.

Pathologic Examination—Peripancreatic lymph node with metastatic carcinoma (Fig 5).

Postoperatively, the patient did poorly, became even more jaundiced, but recovered sufficiently to leave the hospital on the seventeenth postoperative day.

Case 4—Hosp No 181636 E Z, white, female, age 56, was admitted to the hospital, June 17, 1935, complaining of right upper quadrant abdominal pain with radiation to back and right shoulder, on and off for past four weeks. Pain most severe after meals and accompanied by belching. Morphine given on several occasions to relieve attacks of colic. No jaundice or acholic stools. Occasional similar attacks during past five years. Cholecystostomy had been performed 24 years ago for cholelithiasis. Typhoid fever as a child. Thyroidectomy six years before present admission. Physical examination revealed rigidity in both upper abdominal quadrants, most marked on the right side. Tenderness on pressure over region of gallbladder beneath right costal margin. *Preoperative Diagnosis* Acute exacerbation of chronic cholecystitis.

Operative Pathology—An inflamed gallbladder in a maze of adhesions. The ampulla was in close proximity to the second portion of the duodenum and there was marked pericholecystitis. A large ovoid stone was impacted in the cystic duct. Some cirrhosis of liver. The rest of the alimentary tract was apparently negative.

Procedure—Cholecystectomy.

Pathologic Examination—Gallbladder wall dull and granular. Wall moderately thickened. Serosa is thickened and fibrous, muscularis hypertrophied, and wall is infiltrated with plasma cells, mononuclear cells, and some polymorphonuclear leukocytes. Mucosa is diffusely ulcerated (Fig 6). *Pathologic Diagnosis* Chronic and acute cholecystitis. Ulcerative cholecystitis.

The postoperative course was satisfactory except for a notation on the chart on the tenth day stating that there was slight icterus. Patient discharged in good condition with wound healed on fourteenth day following operation, July 2, 1935.

Subsequent Course—The pain in right upper quadrant with radiation to the back persisted after patient was discharged and continued until readmission, September 9, 1935. No jaundice. Hospitalization was advised solely because of the persistent pain, and it was the impression that a common duct stone had been overlooked at the first operation, or that a malignancy was present. The preoperative diagnosis on the operative sheet was "carcinoma of the stomach (?)".

Operative Pathology—Stomach, duodenum and intestines normal. Numerous adhesions about the gallbladder bed. Common duct was exposed and found to be dilated. Stump of the cystic duct was distended and contained debris and several calculi. The pancreas was markedly enlarged from the head extending down toward the tail.

Procedure—Biopsy of tissue from region of head of pancreas taken. Choledochotomy performed and clear bile aspirated. A large T-tube was inserted into the common duct.

Pathologic Examination—Specimen consists of tissue measuring 2x2x1.5 cm, irregularly lobulated, gray and pink. Tissue said to come from pancreas. Sheets of epithelial cells are imbedded in a scant hyalinizing fibrous connective tissue stroma, densely infiltrated with round cells, mononuclear cells and polymorphonuclear leukocytes. The

peripheral cells have a palisade arrangement. The nuclei are large, vesicular, hyperchromatic, and an occasional mitotic figure is seen (Fig 7). *Pathologic Diagnosis* Carcinoma, metastatic.

Postoperatively, the patient had a satisfactory course, drained bile and was able to leave the hospital on the eighteenth day after operation.

Case 5—Hosp No 191379. M. M., white, female, age 58, entered the hospital, May 25, 1936, because of cramp-like abdominal pain, nausea and vomiting which had begun 16 days previously. Two or three days following onset of pain, urine became dark in color, stool gray, and skin jaundiced. Two or three days prior to admission, the icterus appeared to be less intense. Past history was entirely negative for previous similar attacks. Physical examination revealed a thin, undernourished woman, lying comfortably in bed. There was moderate tenderness and muscle spasm in the epigastrium



FIG 6—Path No 812A. Photomicrograph showing area of acute inflammation in gallbladder wall ($\times 200$).

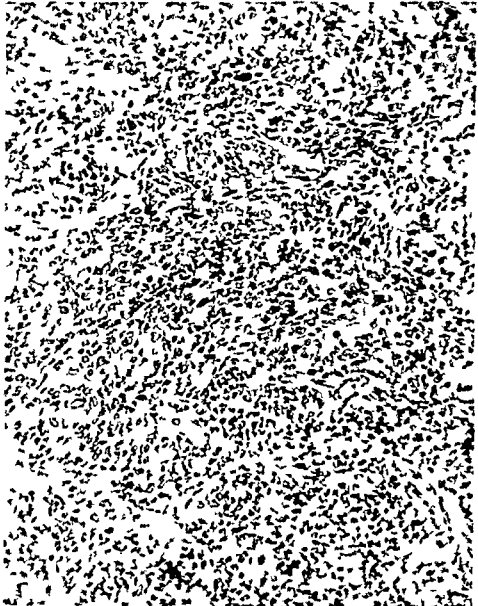


FIG 7—Path No 812B. Photomicrograph of a biopsy taken from the region of the head of the pancreas showing diffuse carcinoma ($\times 290$).

and right upper quadrant of abdomen. A rounded, tender mass, the size of a man's fist, was palpated three fingers' breadth below the right costal margin. A preoperative diagnosis of obstructive jaundice due to common duct stone was entertained and the patient was operated upon the day following entrance into the hospital.

Operative Pathology—Moderately distended gallbladder showing evidence of acute inflammation. No evidence of any neoplasm or calculi. There was a moderately enlarged head of the pancreas which did not give the impression of malignancy. Digestive tract normal. *Postoperative Diagnosis* Acute cholecystitis, chronic pancreatitis.

Procedure—Cholecystostomy. Portion of gallbladder wall taken for microscopic examination.

Pathologic Examination—Specimen consists of soft, gray tissue, 1.2 x 1.0 x 0.6 cm in diameter. Part of the mucosal surface is thrown into folds covered by cylindric cells. There is a marked increase of connective tissue of the tunica propria as well as of the intermuscular and perimuscular connective tissue. These are infiltrated with extravasated blood, small round cells, large mononuclear cells and polymorphonuclear leukocytes (Fig 8). *Pathologic Diagnosis* Acute and chronic cholecystitis.

Postoperative course was fairly satisfactory, although for the first few days there

was rather little bile drainage. The wound healed and the patient was discharged with a biliary fistula on the fifteenth day after operation, June 10, 1936. On the day prior to discharge, temperature rose to 104° F, but returned to normal within a few hours.

Subsequent Course—Drainage of greenish bile through the abdominal fistula persisted following discharge from the hospital. Weakness and loss of 21 pounds in weight occurred during the interval. At no time, from discharge on June 10 to readmission on November 22, did the patient regain normal or approximate normal health. Stools were constantly clay-colored. The patient returned to the hospital because of persistent, slight icterus and continued weight loss. She appeared emaciated, but otherwise no significant physical findings were observed. No abdominal masses palpable. Fistula was lined by granulation tissue and was draining bile. Operation was deemed advisable be-



FIG 8—Path No 4010 Photomicrograph showing acute cholecystitis (x200)



FIG 9—Path No 5697 Photomicrograph showing acute inflammation of the gall bladder wall (x270)

cause it was thought that a common duct stone had been overlooked at the first operation or that a malignancy of the head of the pancreas was present.

Operative Pathology—Numerous pericholecystic adhesions. Foramen of Winslow partially patent. A large, nodular head of the pancreas with a prolongation upward along the common duct was felt. Common duct contained no calculi. *Postoperative Diagnosis*. Carcinoma of head of the pancreas.

Procedure—Cholecystoduodenostomy.

The patient made a satisfactory operative recovery. Bile did not drain through the wound and icterus decreased. Stools began to show bile, thereby demonstrating a functioning cholecystoduodenostomy. Patient left hospital on the seventeenth postoperative day.

Case 6—Hosp No 195095. D B, white, female, age 46, was admitted to the hospital, September 30, 1936, because of severe colicky right upper quadrant abdominal pain of two days' duration. Pain radiated to the back and was associated with nausea and vomiting. Temperature had been elevated to 102° F, and there had been several chills. Belching and aversion for fatty foods for many years. Physical examination showed an acutely ill patient complaining of abdominal pain. Muscular spasm and marked tenderness in the epigastrium and right upper quadrant of the abdomen was noted. No masses. No jaundice or history of jaundice. A diagnosis of acute exacerbation of a chronic

cholecystitis was made and the patient was subjected to surgery on the second day after admission

Operative Pathology—Large, tense distended gallbladder with thickened wall, partially embedded in liver substance. There appeared to be anomalous vessels arising from the cystic artery. A stone was found impacted in the cystic duct. Common duct and head of pancreas appeared normal. No other pathology noted.

Procedure—Cholecystectomy. An excess amount of bleeding was encountered during the operation.

Pathologic Examination—The mucosal surface is thrown into folds covered with tall columnar cells. There are in places invaginations of the mucosa which extend to the somewhat hypertrophied muscular coat. The lamina propria is broadened by edema and is infiltrated by small round cells, large mononuclear cells, some eosinophils and polymorphonuclear leukocytes. A similar cellular infiltration, though less marked, is seen in the intermuscular and perimuscular connective tissues. In the latter, some vessels show margination of white blood cells and there are small foci of extravasated blood (Fig. 9).

Pathologic Diagnosis Acute and chronic cholecystitis.

Postoperatively, the patient did poorly. Temperature remained high with daily elevations to 102° F. The wound became infected and drained thin, gray pus and bile. However, from the eleventh to the fourteenth day, the temperature subsided and the patient was considered sufficiently recovered to discharge, October 18, 1936.

Subsequent Course—On the day following discharge, temperature rose to 104° F. A deep abscess was evacuated from area in wound at the site of the drain. A small amount of bile drained for the next two to three days, but stopped spontaneously. Temperature, anorexia and malaise continued despite drainage of the wound abscess. A mass in the right upper quadrant of the abdomen extending down toward the right iliac spine was palpated. The patient was readmitted two weeks following discharge. It was thought that a subhepatic abscess was in process of formation but that operation should be deferred until further localization had occurred. The patient was observed for the next four weeks, during which time she became progressively weaker, lost weight, and ran a temperature ranging from 102° to 104° F. The abdominal mass became larger, but instead of localizing, it appeared to become more diffuse. On December 4, 1936, an oblique incision in the right flank was made.

Operative Pathology—No pus was found. Exploration of the retroperitoneal space revealed a markedly enlarged right kidney with induration of the perirenal fat, and boggy and thickness extending up above the kidney and toward the liver, and retroperitoneally below the kidney down along the course of the iliopsoas muscle. *Postoperative Diagnosis* Retroperitoneal phlegmon.

Procedure—Insertion of rubber drains.

The patient responded very poorly to operation. Despite blood transfusion and other supportive measures, the patient went into shock and expired the day following operation.

Autopsy—Sarcoma of iliopsoas muscle, right, metastasis to regional, abdominal, retroperitoneal, axillary lymph nodes, spleen, pancreas, ovary, peritoneum, ureters, thyroid, and to the vertebrae. The pancreas measured 21×4×2 cm, weighed 120 Gm and showed sarcomatous metastases. The head of the pancreas was surrounded by large, pale-gray lymph nodes measuring up to 3×3 cm in size (Fig. 10).

Case 7—Hosp. No. 216288. S. A., white, male, age 46, was admitted to the hospital, February 26, 1938, because of colicky right upper quadrant abdominal pain and nausea, particularly severe the past ten days. He had noticed anorexia, aversion for fats, weight loss and weakness for the past month. Six years ago, he had had a right hemicolectomy for carcinoma of the ascending colon. His health had been excellent since then and his bowel function had been normal. For ten days prior to admission, his skin became jaundiced and pruritus marked. Physical examination revealed jaundiced skin and evidence of marked weight loss. Liver was enlarged to two fingers' breadth below the right costal margin. Tenderness was extreme in the gallbladder area, with moderate

muscle rigidity No other masses palpable *Preoperative Diagnoses* (1) Metastases to liver secondary to carcinoma of colon, or (2) acute cholecystitis with cholelithiasis and common bile duct obstruction Operation was performed, March 15, 1938

Operative Pathology—Omentum intimately adherent to the anterior parietal wall and gallbladder Gallbladder was enlarged, firm, distended and noncompressible Wall was injected, opaque, thickened and edematous Lumen contained light mucobile and no calculi Cystic and common ducts were normal to palpation Liver enlarged to two fingers' breadth below costal margin, the surface was smooth and no nodules were noted Pancreas and duodenum normal Adjacent to the common duct, three distinct soft nodes the size of almonds, not exerting pressure on the common duct, were noted *Postoperative Diagnosis* Acute cholecystitis, noncalculous

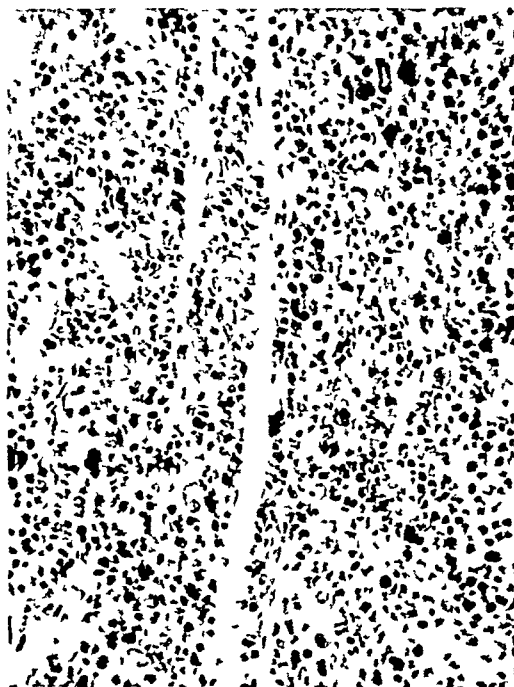


FIG 10—Path No 2798 Photomicrograph showing rhabdomyosarcoma, section taken from upper end of right iliohypogastric muscle (X280)



FIG 11—Path No 810 Photomicrograph showing acute cholecystitis (X270)

Procedure—Cholecystectomy

Pathologic Examination—The mucosal surface of the gallbladder is thrown into coarse and delicate folds There are occasional infoldings of the epithelium extending into the greatly hypertrophied muscular coat Connective tissue of the tunica propria is greatly increased in amount and is infiltrated with small and large mononuclear cells, eosinophils, plasma cells and polymorphonuclear leukocytes This cellular infiltration is also seen in the intermuscular and perimuscular connective tissue Some of the blood vessels show margination of the white blood cells A similar infiltration is also seen in the serosa which is broadened by edema (Fig 11) *Pathologic Diagnosis* Acute and chronic cholecystitis

The patient did fairly well postoperatively for the first two weeks Jaundice slowly cleared and the wound healed, despite a large hematoma and wound infection On the twenty-second day after operation, the patient developed a spontaneous biliary fistula which drained large quantities of bile His course was further complicated by a diffuse pyoderma caused by *Staphylococcus aureus* He was kept in the hospital for 69 days after operation, during which time his biliary sinus drained intermittently *Staphylococcus* vaccine was given in large quantities to control his diffuse, pustular skin eruptions

Subsequent Course—From the date of discharge, May 23, until August 20, he was

evidently in fairly good health. However, his biliary fistula then stopped draining and he became jaundiced. This lasted for two weeks and subsided spontaneously. He developed jaundice again, September 26, which persisted until readmission to the hospital, October 10. The day prior to hospitalization, he suffered moderate right upper quadrant abdominal pain and had a temperature of 102° F. Physical examination revealed slight tenderness in the region of the scar in the right upper quadrant but no masses. A pre-operative diagnosis of common duct stone was made. The patient was treated conservatively in an attempt to better prepare him for the surgical procedure. He was operated upon, November 8, 1938.

Operative Pathology—The common duct was found markedly dilated. It was opened and probed in both directions but no calculi were found. The duodenum was then opened and the common duct explored through the papilla of Vater but still no stones were found. The duodenum was closed and a T-tube inserted into the common duct. Postoperatively, the patient developed a duodenal fistula, went downhill rapidly, and died on the sixth day after operation.

Autopsy—A carcinoma was found which originated in the terminal end of the com-



FIG 12—Path No 38-165 Photomicrograph showing section of carcinomatous tissue from the common bile duct (×180)



FIG 13—Path No 2974 Photomicrograph showing acute inflammatory process in wall of gallbladder (×195)

mon bile duct and extended into the duodenum. There were metastases to regional lymph nodes. The duodenum was perforated at the site of its incision with a resultant retroperitoneal cellulitis and areas of fat necrosis. No pathology was noted at the site of anastomosis of the ileum to the transverse colon (Fig 12).

Case 8—Hosp No 215187 H T, white, female, age 68, was admitted to the hospital, September 13, 1938, complaining of constant upper abdominal pain, anorexia and weight loss of two months' duration. Icterus and pruritus noted for past two weeks. For about one year patient had been having attacks of cramp-like left upper quadrant pain radiating to the epigastrium, the right upper quadrant and around to the back. Physical examination revealed cachexia, jaundice, and voluntary upper abdominal muscle spasm. No masses palpable. A clinical diagnosis of either carcinoma of the head of the pancreas or common bile duct calculus was made, and the patient was operated upon, September 24, 1938.

Operative Pathology—An inflammatory mass including the omentum, transverse

colon, ileum and gallbladder was encountered. Pancreas slightly enlarged but not firm or nodular. The gallbladder, after being released from the surrounding adhesions, was found to be grayish-yellow, the wall was necrotic and considerably thickened. In the lumen, yellow, purulent material was present. No stones found either in gallbladder or cystic duct. Common duct not visualized because of adherent surrounding tissues. The liver extended three fingers' breadth below the costal margin. *Postoperative Diagnosis* Empyema of the gallbladder.

Procedure—Cholecystostomy. A small portion of the gallbladder wall was taken for microscopic study.

Pathologic Examination—The mucosal surface is completely missing. The wall is greatly thickened. In places it is densely infiltrated by many small round cells, large mononuclear cells, plasma cells and some polymorphonuclear leukocytes. Numerous thin-walled capillaries distended with blood are seen scattered throughout the entire wall. No

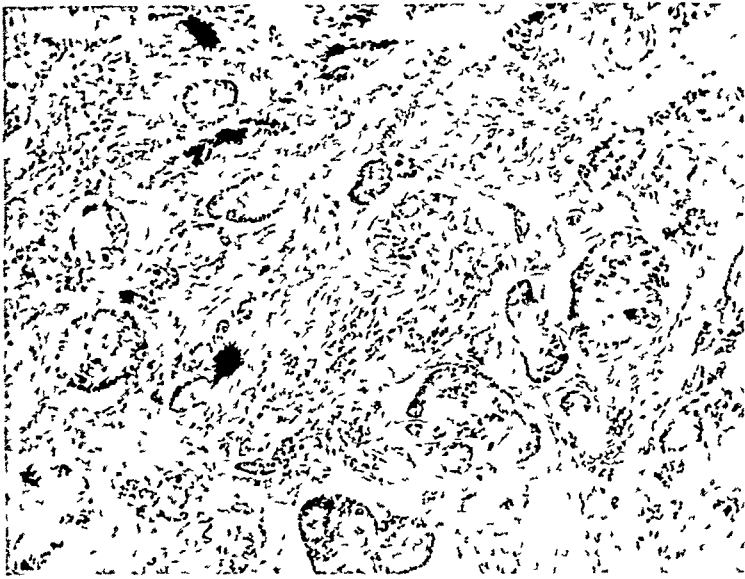


FIG 14—Path No 38-142. Photomicrograph showing section of carcinomatous tissue from common bile duct ($\times 115$).

neoplastic cells seen (Fig 13). *Pathologic Diagnosis* Acute and chronic inflammation of gallbladder.

The patient went rapidly downhill, and expired three days following operation.

Autopsy—At its junction with the cystic duct, the common duct shows a circular, gray, firm mass, 2 cm in width and 3 cm in length. The lumen at this point shows a granular surface and its caliber is narrowed so that escape of bile is obstructed. Microscopic examination of tissue from common bile duct shows the surface to be composed of folds of necrotic tissue in which ghosts of cell structures are seen. There are acinar and duct-like structures lined by low cuboidal and cylindric cells which vary in size, shape and chromatin content of their nuclei. Occasional mitotic figures are seen. Many of the lining cells project beyond the basement membranes into the surrounding fibrous tissue. Clumps of cells are also seen within endothelial-lined spaces. The cytoplasm of these cells is predominantly abundant and finely granular. The nuclei are either vesicular, round or dark staining and bizarre-shaped (Fig 14). *Pathologic Diagnosis* Carcinoma of common bile duct.

COMMENT—Seventy-three patients with carcinoma of the head of the pancreas and 17 patients with carcinoma of the common bile duct entered the hospital from 1913 to 1938.* Of these 90 patients, 19 had cholecystitis,

* Unpublished data, Jewish Hospital, Brooklyn, N. Y.

as proved either by operation or roentgenographic evidence of a nonfunctioning gallbladder. Seven of the eight cases of acute cholecystitis, herein reported, are part of this group of 19 cases.

As the majority of patients who develop carcinoma of the head of the pancreas or common bile duct give no history of preceding gallbladder infection, this factor has been considered of little etiologic significance. Ransom,¹ in a thorough review of 89 operative cases of carcinoma of the head of the pancreas and extrahepatic bile ducts, found antecedent gallbladder pathology in 15. Rives, Romano and Sandifer² encountered gallbladder pathology in eight of their 96 patients with carcinoma of the pancreas. Eusterman and Wilbur³ found that six of 88 nonjaundiced patients with carcinoma of the pancreas also had gross cholecystitis. Marshall⁴ reported that 26 of his 49 patients with carcinoma of the extrahepatic bile ducts had gallbladder disease. None of these authors suggests that the cholecystitis played an important etiologic rôle, although all mention the possibility of some causal relationship.

The high incidence of gallbladder disease observed in our cases may possibly be attributed to the fact that biliary infection occurs so frequently in Jewish people. It is interesting to note that 18 of the 19 patients with antecedent cholecystitis were Jewish. Furthermore, although carcinoma of the pancreas is twice as common in men as in women, we find that there are more women than men in the group with a preceding cholecystitis. This is explained by the fact that cholecystitis has a much greater incidence among women.

We agree with the authors quoted, that cholecystitis probably plays an unimportant rôle in the etiology of a neoplasm of the common duct or head of the pancreas. However, it has long been recognized that disturbances in tissue tension resulting from a surgical procedure can accelerate the growth of a neoplasm. As the time interval between the acute cholecystitis and the discovery of the malignancy was so short in our series of cases, one might hypothesize that the gallbladder infection caused the underlying tumor to grow with inordinate rapidity. Conversely, it is reasonable to assume that the presence of a malignant lesion permitted the infectious process in the gallbladder to take a firmer hold than it would have under ordinary circumstances.

Scant consideration has been given to the subject of *acute* cholecystitis as a lesion occurring during the early course of carcinoma of the pancreas or common bile duct. Ransom's allusion to a case of empyema of the gallbladder in a patient with carcinoma of the head of the pancreas was the only instance we encountered in reviewing the literature. Since chronic cholecystitis has been noted so frequently as an antecedent condition in neoplasms of the common duct and head of the pancreas, we feel that it is only natural to expect that a certain number of these cases will be complicated by an acute cholecystitis. Furthermore, all of the factors which would cause a chronic cholecystitis to become an acute cholecystitis are present in the

eight cases which we have described in this report. Thus, biliary stasis was increased because of the compression of the common duct by the neoplasm, intraductal pressure became greater due to interference with free biliary drainage, the blood supply to the gallbladder wall may have been embarrassed by pressure from the enlarging head of the pancreas or tumor in the common duct, and the cystic artery or cystic veins might have been compressed by enlarged lymph nodes or by surrounding edema.

Infection finds a fertile soil for taking root in the presence of stasis, increased intraductal pressure and partial common duct obstruction. If there has been a preexistent chronic infection of the gallbladder, it is even easier for reinfection to take hold. When one or more of these phenomena occurs, an otherwise quiescent chronic cholecystitis may become markedly acute. A cystic duct stone, which had previously produced only partial block, may cause complete obstruction with subsequent empyema or gangrene. An exacerbation of a chronic cholecystitis may be precipitated by edema of the neck of the gallbladder, insufficient blood supply, or venous congestion resulting from impingement by the neoplasm. It is our opinion that such was the sequence of events in these eight cases.

The short interval, varying from a few days to 12 weeks, between the operation for acute cholecystitis and the development of symptoms of the underlying malignancy, suggests that the neoplasm must have been present at the time of the first operation. It is hardly conceivable that the malignancy could have developed in such a short space of time. In retrospect, we find that indications of the underlying tumor were present at the first operation in several of the cases, but that the severity of the acute findings led to the misinterpretation of these clues. Edema and enlarged lymph nodes were noted by the operating surgeons, but in the presence of the acute gallbladder pathology, they were interpreted as being inflammatory in origin.

These cases offer an interesting problem from a surgical point of view, for it is considered meddlesome surgery to carry out extensive abdominal exploration in the presence of an acute or suppurative lesion. It is, therefore, reasonable to assume that the underlying lesions were overlooked, first, because they were not suspected, and second, because the findings were those of an acute inflammatory process. One can merely suggest that when acute changes in the gallbladder are encountered, a careful search be made in the region of the common duct and head of the pancreas, providing that such exploration does not engender spread of the infectious process.

SUMMARY AND CONCLUSIONS

(1) Eight cases of acute cholecystitis occurring during the early course of neoplastic common bile duct obstruction are presented.

(2) In all cases, the gallbladder showed acute inflammation. In all cases, a malignancy which produced common duct obstruction was eventually discovered. The time interval between acute cholecystitis and symptoms referable to the malignancy varied from a few days to 12 weeks.

(3) In no case did the surgeon suspect a malignancy upon observing the acute cholecystitis at the operating table

(4) The mechanism involved in the production of the acute exacerbation of the cholecystitis is discussed. The acute attack is attributed to the combined effects of circulatory changes and progressive common duct obstruction upon a gallbladder which is already diseased.

(5) Emphasis has been placed on the dangers of not recognizing the underlying neoplasm because of the existing acute inflammatory lesion.

We should like to express our appreciation to Dr. D. M. Grayzel for his assistance in assembling the pathologic material.

REFERENCES

- ¹ Ransom, H. K. *Am Jour Surg*, **40**, 264-281, April, 1938.
- ² Rives, J. D., Romano, S. A., and Sandifer, F. M., Jr. *Surg, Gynec and Obstet*, **65**, 164-177, August, 1937.
- ³ Eusterman, G. B., and Wilbur, D. L. *South Med Jour*, **26**, 875-883, October, 1933.
- ⁴ Marshall, J. M. *Surg, Gynec and Obstet*, **54**, 6-12, January, 1932.

STUDIES ON THE ABSORPTION OF SULFANILAMIDE FROM THE LARGE INTESTINE

RESULTS FOLLOWING THE ADMINISTRATION OF SUPPOSITORIES

ROBERT TURELL, M D , A W MARTIN MARINO, M D ,

AND

LOUIS NERB, PH D

BROOKLYN, N Y

FROM THE DIVISION OF PROCTOLOGY, DEPARTMENT OF SURGERY, ERNST K. TANNER, DIRECTOR AND THE LABORATORIES
OF THE BROOKLYN HOSPITAL, BROOKLYN, N Y

OUR recent experimental studies indicate that there is good absorption of sulfanilamide from the rectum as well as the colon.^{1 2} In our studies on the absorption from the human large intestine,² warm (30° C) 1 per cent solutions of sulfanilamide were employed. In normal individuals approximately 9 mg of combined sulfanilamide per 100 cc of blood were found following the rectal administration of 7 Gm of the drug over a period of 24 hours. After about 19 Gm of sulfanilamide had been given over a period of 72 hours, approximately 11 mg of combined sulfanilamide per 100 cc of blood were found.

In order to determine whether sulfanilamide is absorbed directly from the colon, or whether it passes into the ileum and is absorbed there, the same series of investigations were repeated in a subject who had no communication between the small intestine and the colon. A permanent ileostomy with exclusion had been performed in November, 1936, for a rapidly progressive chronic ulcerative colitis. Following operation, there had been an arrest of the disease except for the recurrent development of polypi. Although the colon in this case could not be considered normal, it afforded an excellent opportunity for the study of absorption of sulfanilamide from the large intestine. After the rectal administration of 14 Gm of sulfanilamide over a period of about 65 hours, the blood showed a concentration of 15 mg of combined sulfanilamide per 100 cc.

In order to investigate the absorption of the drug from the rectum, we utilized a subject who had had a resection of the sigmoid for a carcinoma. The proximal portion of the sigmoid had been brought out as a colostomy and the rectal stump had been closed and covered with peritoneum, after the method of Devine,³ leaving a defunctioning rectal pouch. After the administration of 18 Gm of sulfanilamide in solution into the rectal pouch over a period of three days, the concentration in the blood was 11 mg of combined sulfanilamide per 100 cc. This experiment definitely established the fact that sulfanilamide in solution is absorbed from the isolated rectum.

The following are the results of the studies on absorption of sulfanilamide

Submitted for publication June 1, 1939

from the rectum and colon when given in suppository form. These studies were conducted under the same experimental conditions as described in our previous paper.² The blood concentrations were determined by the method of Marshall, as modified by Marshall and Litchfield.⁴

Protocol 1—L. A., white, male, age 52, was admitted to the Brooklyn Hospital, December 4, 1938, with a diagnosis of fistula in ano. Examination was otherwise normal and he was considered suitable for this study. One gram of sulfanilamide incorporated in gelatin-glycerine suppositories was given at three-hour intervals for two doses. The concentration of the blood three hours after the first dose was 1 mg free sulfanilamide per 100 cc. Three hours after the administration of the second dose, 2 mg free sulfanilamide per 100 cc of blood were found. This procedure was repeated the following day. Three hours after the administration of the first gram of sulfanilamide, the concentration of the blood was 1.5 mg free sulfanilamide, and three hours after the administration of the second dose, it was 2.5 mg free sulfanilamide per 100 cc of blood.

We then studied absorption of sulfanilamide in suppository form, first from the colon and then from the rectum. In these experiments (Protocol 2A and 2B) we again employed the subject with the isolated rectal pouch.²

Protocol 2A—Two suppositories, each containing 0.5 Gm of sulfanilamide, were introduced into the rectal pouch every four hours, the midnight dose being omitted. After 5 Gm of sulfanilamide had been given, a trace of the drug was noted in the blood, after 10 Gm had been introduced, 1 mg free and 1 mg conjugated sulfanilamide were observed per 100 cc of blood and after a total of 15 Gm had been given, 1.5 mg free, and a trace of conjugated sulfanilamide were found per 100 cc of blood. The investigation was terminated at this stage because of reasons unrelated to the experiment. Traces of sulfanilamide in the blood were observed about 30 hours after the last dose had been given.

Comment—It is evident that sulfanilamide incorporated in suppositories is poorly absorbed from the isolated rectal pouch. The solution of sulfanilamide was absorbed well.² Thus, after the administration of 6 Gm of 1 per cent solution of sulfanilamide over a period of 24 hours, 3 mg free sulfanilamide per 100 cc of blood was found, none of the conjugated form of sulfanilamide was present. After the administration of a total of 12 Gm over 48 hours, the concentration of the blood was 3.5 mg free and 1.5 mg conjugated sulfanilamide per 100 cc. As already recorded, after a total of 18 Gm of sulfanilamide had been given, 6 mg free and 5 mg conjugated sulfanilamide were observed per 100 cc of blood.

Protocol 2B—After preliminary determinations had shown no evidence of sulfanilamide, a study of absorption of sulfanilamide from the colon was begun. Two suppositories, each containing 0.5 Gm of sulfanilamide, were introduced into the colostomy stoma every four hours, day and night. The patient was instructed to lie on his back for one hour after the insertion of the suppositories. In spite of this precaution, parts of the medication were expelled at times. After 6 Gm of sulfanilamide had been given, 2 mg of free sulfanilamide were found in each 100 cc of blood, after the administration of 12 Gm, the concentration of the blood was 2.5 mg free and 1.5 mg conjugated sulfanilamide, and after a total of 18 Gm of sulfanilamide had been administered, 3.5 mg free and 1.5 mg conjugated sulfanilamide were found per 100 cc of

blood The concentration of the blood, 24 hours after cessation of therapy, was 1 mg free and 1.5 mg conjugated sulfanilamide per 100 cc

Comment—This experiment indicates that sulfanilamide in suppository form is absorbed better from the colon than from the rectum. Reliable comparative figures for absorption of sulfanilamide in solutions were not obtained owing to the fact that the solution was frequently expelled from the colostomy stoma.

Protocol 3A—H. H., Negro, male, age 20, was admitted to the Brooklyn Hospital because of a left bubo and right inguinal lymphadenopathy. The Frei test, using three human antigens, gave strong positive reactions. A complete examination and laboratory tests disclosed that he was otherwise normal, and suitable for this study. Forty-eight hours after the bubo had been aspirated, a course of sulfanilamide therapy was instituted. One ounce of castor oil, followed by a colonic irrigation, was given one day before this study was begun. Two suppositories, each containing 0.5 Gm of sulfanilamide, were administered every four hours, day and night. After the administration of 7 Gm of sulfanilamide, the concentration of the blood was 1 mg free and 1 mg conjugated sulfanilamide per 100 cc; after 13 Gm had been given, the concentration of the blood was 2.5 mg free per 100 cc; none of the conjugated sulfanilamide was present (some of the medication was expelled on two occasions); after 19 Gm of sulfanilamide had been given, 4 mg free and 2 mg conjugated sulfanilamide were found in each 100 cc of blood; and after a total of 25 Gm of sulfanilamide had been administered, the concentration of the blood was 6 mg free and 2 mg conjugated sulfanilamide per 100 cc of blood. Blood, drawn 12 hours after cessation of therapy, and eight hours following a colonic irrigation, showed 3 mg free sulfanilamide per 100 cc. Twenty-four hours later, 1 mg free sulfanilamide was found. Traces of sulfanilamide were noted 48 hours after cessation of therapy.

Protocol 3B—After preliminary determinations of the blood had shown no evidence of sulfanilamide, H. H. was given 100 cc of a 1 per cent solution of sulfanilamide rectally every four hours, day and night. After 6 Gm of sulfanilamide had been given, the concentration of the blood was 6 mg free and 1 mg conjugated sulfanilamide per 100 cc; after 12 Gm had been administered, 8 mg free and 2 mg conjugated sulfanilamide per 100 cc were noted; after the administration of 18 Gm of sulfanilamide, again, 8 mg free and 2 mg conjugated sulfanilamide per 100 cc of blood were obtained; and after a total of 24 Gm of the drug had been given, the concentration of the blood was 3.5 mg free and 4 mg conjugated sulfanilamide per 100 cc. Blood drawn 24 hours after cessation of therapy revealed 4 mg free and 1.5 mg conjugated sulfanilamide per 100 cc. After 48 hours, the concentration in the blood was 1.5 mg free and 1 mg conjugated sulfanilamide.

Comment—Higher concentrations of sulfanilamide in the blood were noted in this experiment than in Protocol 3A, proving that greater absorption of sulfanilamide occurs when the drug is administered in solution than in suppository form.

Protocol 4—E. W., white, female, age 28, had had chronic ulcerative colitis for four years. On March 11, 1939, she was sent to the Brooklyn Hospital with signs of hemoperitoneum. At operation, a ruptured corpus luteum in the left ovary with massive hemorrhage in the peritoneal cavity was found. After two blood transfusions of 500 cc each, the hemoglobin value was 80 per cent (Sahli). On the twelfth postoperative day she was considered suitable for the study of absorption of sulfanilamide from the large intestine. Two suppositories each containing 0.5 Gm of sulfanilamide, were given every four hours, day and night. After the administration of 6 Gm of sulfanilamide,

the concentration of the blood was 3 mg free and 1 mg conjugated sulfanilamide per 100 cc, after the administration of 12 Gm, the concentration of the blood was 4 mg free and 2 mg conjugated, after 18 Gm of sulfanilamide had been given, the concentration of the blood was 7 mg free and 2 mg conjugated, and after a total of 24 Gm of sulfanilamide was given, the concentration of the blood was 6 mg free and 1 mg conjugated sulfanilamide per 100 cc. The blood concentration 24 hours after cessation of sulfanilamide therapy was 3.5 mg free and 1.5 mg conjugated sulfanilamide per 100 cc. After 48 hours, the concentration of the blood was 1 mg free and 1.5 mg conjugated sulfanilamide per 100 cc.

Comment—Cyanosis and nausea were observed. This is the first instance of nausea seen in our studies of absorption of sulfanilamide from either the normal or diseased large bowel.

Proctosigmoidoscopic studies following the rectal administration of sulfanilamide showed no changes in the normal mucosa of the rectum or colon.

SUMMARY AND CONCLUSIONS

(1) Evidence is presented to show that sulfanilamide is absorbed from the rectum and colon when given either in solutions or in suppositories.

(2) Higher concentrations of sulfanilamide were noted in the blood, hence greater absorption, following the rectal administration of sulfanilamide in solution.

(3) The rectal route of administration of sulfanilamide is recommended whenever the oral route cannot be utilized. The same total dosage may be employed for the rectal as for the oral administration.

The sulfanilamide used in these experiments was supplied by the Medical Research Department, Winthrop Chemical Company.

REFERENCES

- ¹ Nerb, L., Turell, R., and Marino, A. W. M. Absorption of Sulfanilamide from the Rectum and Colon of Rabbits. *Brooklyn Hosp Jour*, 1, 88-89, April, 1939.
- ² Turell, R., Marino, A. W. M., and Nerb, L. Observations Concerning the Absorption of Sulfanilamide from the Large Intestine in Man. An Experimental Study. *Brooklyn Hosp Jour*, 1, 90-93, April, 1939.
- ³ Devine, H. Operation on Defunctioned Distal Colon. *Surgey*, 3, 165-194, February, 1938.
- ⁴ Marshall, E. K., Jr., and Litchfield, J. T., Jr. The Determination of Sulfanilamide. *Science*, 88, 85-86, July 22, 1938.

STRUMA LYMPHOMATOSA (HASHIMOTO)

REPORT OF TWO CASES

J E KEARNS, JR, M D

EVANSTON, ILL

THE FOLLOWING PATIENTS with "struma lymphomatosa" (Hashimoto) were seen at the Endocrine Clinics of the Evanston Hospital and Northwestern University. Operations were performed on the services of Doctors Koch and Mason at Passavant Memorial Hospital and Doctor Christopher at Evanston Hospital. One patient is a female in the third decade of life, and is of interest because of her age. The other, a male, almost in his seventieth year, is of extreme interest because nearly 100 per cent of reported, verified lesions occur in women.

The problem of so-called "chronic nonspecific thyroiditis" is still very confusing. Clinically, it seems to have little or no relation to definite previous acute inflammatory lesions. It seems best for the present to consider it of at least three types: Riedel's, or fibrous, Hashimoto's, or lymphoid, and a mixture of these two, or lesions which will fit neither of the above but still show evidence of a chronic process. Some authors doubt the existence of these as actual types and feel that they are but various stages in the same disease. It is not within the scope of this paper to enter this argument. However, we feel there are both clinical and histologic differences sufficient to separate Riedel's¹ and Hashimoto's² types. This is true if one will follow the original, definite descriptions of the lesions by the authors. The reader is referred to the excellent reports by Ewing,³ Graham,⁴ Graham and McCullaugh,⁵ Heitzler,⁶ Lee,⁷ McClintock and Wright,⁸ and Means⁹ for further discussion.

CASE REPORTS

Case 1—M B, female, age 28, married, was born in Wisconsin. She complained of nervousness, weakness, some palpitation and tachycardia, noticed mostly at night. She had had severe frontal headaches, two a day, for the past two months. The inventory by systems was essentially negative. She had jaundice when a child. There was no history of recent weight loss. Menarche at age 17. Menses are regular 28-day type with no pain and of five days' duration. There was one pregnancy with child, living and well, ten months old. No significant family history. The physical findings were: Blood pressure 116/70, pulse 80. The eyes were negative except that the right pupil appeared larger (?) than the left. There was a questionable tremor of the hands, and some dental caries. The heart, lungs, abdomen, and extremities were negative. The thyroid was palpable and firm. Laboratory studies showed: Whole blood cholesterol 163 mg, basal metabolic rates several were about plus 20, with pulse 96 to 88. Wassermann and Kahn, urine, *etc*,

Submitted for publication April 26, 1939

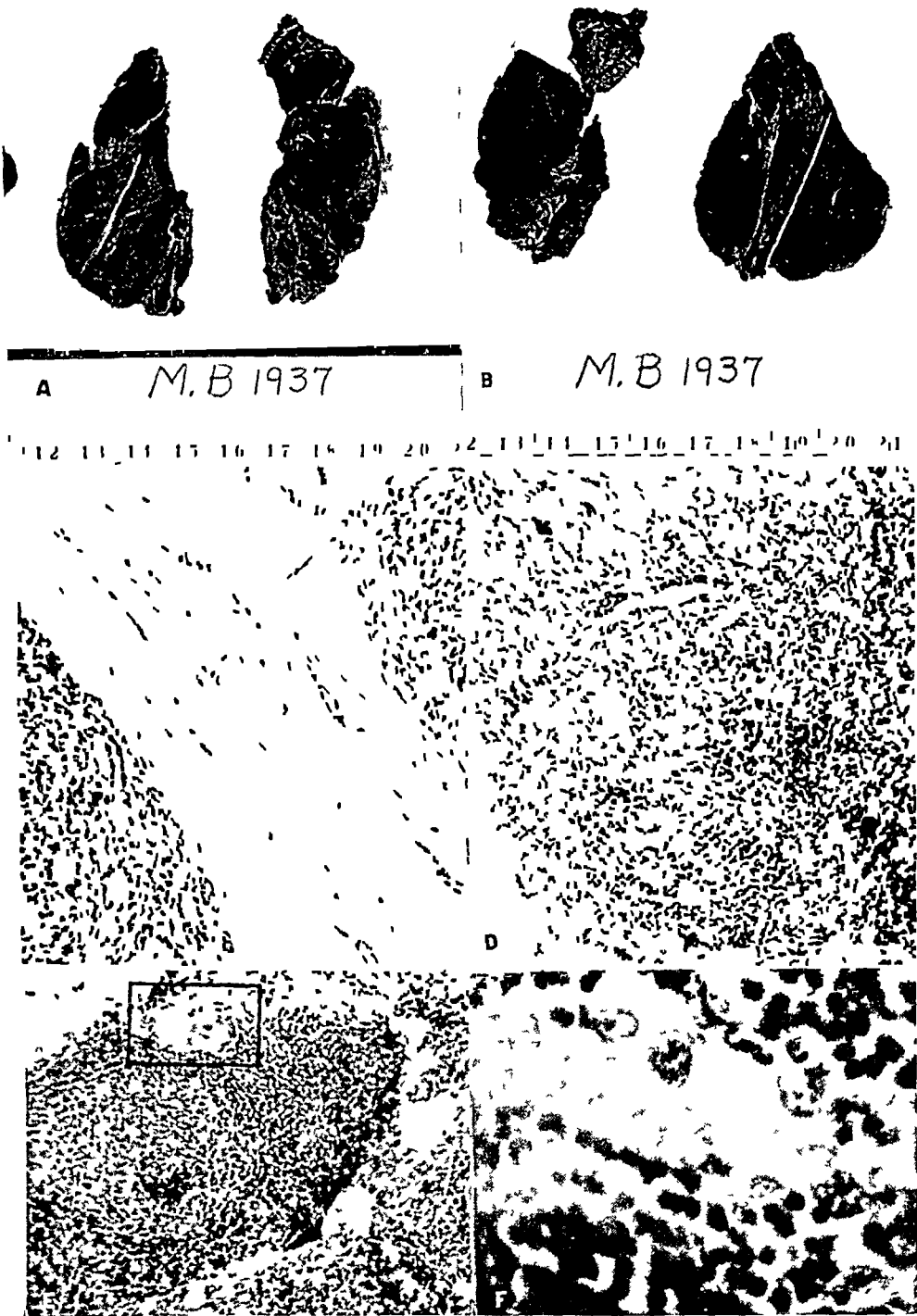


FIG 1—Struma Lymphomatosa Case 1. A Right and left lobes anterior surfaces white and very hard. B Cut sections of lobes showing grayish white surface. C Connective tissue $\times 80$. D Lymph follicle with germinal center $\times 80$. E Lymph cell infiltration and acini with foamy cells, $\times 80$. F High magnification of foamy cells in blocked area $\times 500$.

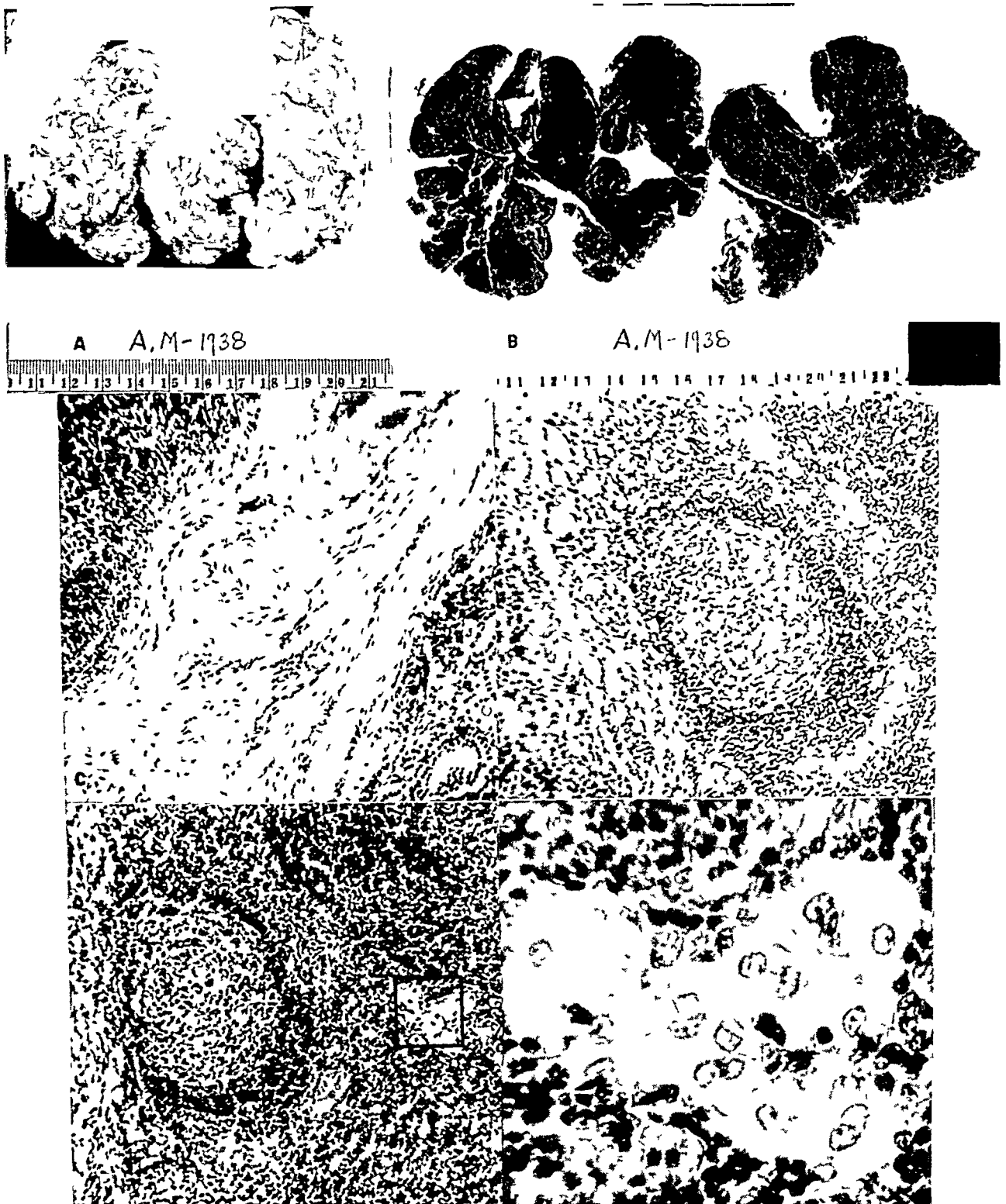


FIG 2—Struma Lymphomatosa Case 2. A, Total thyroidectomy showing interior surfaces of three lobes, B, Cut sections all lobes show mottled grayish white surfaces, C, Connective tissue $\times 80$, D, Lymph follicle with germinal center $\times 80$, E, Lymph cell infiltration and acini with "foamy" cells, $\times 80$, F, Higher magnification of "foamy" cells in blocked area, $\times 500$

were negative. Blood counts were Hemoglobin 72 per cent, red blood cells 4,280,000, white blood cells 5,700, and the electrocardiogram showed normal rate and rhythm. Roentgenologic examination of the chest was normal. The patient was hospitalized before operation and showed no response to Lugol's. At operation the gland was firm, fibrous and adherent. The weight of tissue removed was 24 Gm (Fig 2). She was discharged from the hospital on the ninth postoperative day. One year following operation, this patient is showing symptoms of hypometabolism, but still has a great deal of sympathetonia.

Case 2—A M, male, age 65, a native of Persia. He complained of a mass in the neck with a feeling of tightness (past year), pain in back and shoulder (four months), loss of weight (12 lbs in six years), more irritable and nervous (four months), pain in left leg (five years), difficulty on urinating (intermittently last four months), constipation (years), pain in chest (four to five years), dizziness (past year), cough (six months). Inventory by systems was essentially negative except as above. The physical examination showed Pulse 68, respiration 20, blood pressure 144/84. There was a slight cyanotic tinge to the face with dilatation of veins over upper chest and neck. Dental caries present. The thyroid was enlarged bilaterally and firm. The heart, lungs, and extremities were negative. The abdomen was normal, except that the liver was slightly enlarged. The patient had no thyroid enlargement while living in Persia. He has been a resident of Chicago for 29 years and the goiter developed while here. The clinical impression was that in view of recent growth, symptoms, *etc*, the thyroid should be removed immediately. Laboratory examination showed Kahn negative, blood cholesterol 232 mg, blood count, hemoglobin 80 per cent, red blood cells 4,740,000, white blood cells 8,850. The urine was negative. Several basal metabolic tests were between minus 10 and minus 15. Roentgenologic examination revealed no compression or displacement of the trachea. However, when barium was given by mouth it was seen fluoroscopically to pass, at all times, more to the right than to the left, as though there was some extrinsic mass causing pressure on the left side of the hypopharynx and upper esophagus. Examination of the neck showed slight constriction of the trachea at the point of entry into the thoracic cavity. Of interest are two 'basal rates' taken after admission to the hospital. They were a plus 86 and plus 88 on different days and show the error possible with this test. Following operation there has been progressive hypothyroidism which was apparent before treatment and is being controlled with desiccated thyroid (Fig 2).

In general, the pathologic examination of these two glands is similar. They are those of a hard gland with bilateral enlargement. The cut surface has a slightly granular, grayish-white appearance, mottled by darker areas and lobulated by bands of white connective tissue. The microscopic findings show intense infiltration of the interacinal spaces with lymphocytes and the presence of lymphoid follicles, many of them which have germinal centers. This infiltration may be so great that the acini are entirely obliterated. The acinal cells in some areas are large and appear "foamy." There is an absence of colloid. According to Hertzler,⁶ the "foamy" appearance and the clumping of the acinal cells are a constant feature of this lesion and are sufficient alone to distinguish it from the other types. There are areas of apparent hyperplasia in the glands, probably of a compensatory nature. The connective tissue is usually swollen, poorly stained, and the cells have few nuclei differing from that seen in the Riedel type which forms heavy keloid-like bundles.

Both specimens have been studied by Dr Allen Graham of Cleveland, whose impressions in brief are as follows. In Case 1, the gland is suggestive of an "early" lesion similar to that described by Hashimoto, and in Case 2, the gland is typical for lesions described by Hashimoto.

SUMMARY—Two patients with struma lymphomatosa (Hashimoto) are reported, one present in a male and the other in a young woman.

We wish to thank Doctors Koch, Mason and Christopher for the privilege extended in reporting these cases, and Dr Allen Graham for his help and advice.

BIBLIOGRAPHY

- ¹ Riedel Die chronische, zur Bildung eisenherter Tumoren führende Entzündung der Schilddrüse Verhandl d deutsch Ges f Chir , 25, 101, 1896
- ² Hashimoto, H Zur Kenntniss der lymphomatosen Veränderung der Schilddrüse (Struma lymphomatosa) Arch f klin Chir , 97, 219, 1912
- ³ Ewing, James Neoplastic Disease, Ed 2, 908, Philadelphia, W B Saunders Co , 1922
- ⁴ Graham, A Riedel's Struma in Contrast to Struma Lymphomatosa (Hashimoto) West Jour Surg , 39, 681-689, 1931
- ⁵ Graham, A , and McCullaugh, E P Atrophy and Fibrosis Associated with Lymphoid Tissue in the Thyroid Struma Lymphomatosa (Hashimoto) Arch Surg , 22, 548, 1931
- ⁶ Hertzler, A E Surgical Pathology of the Thyroid Gland Philadelphia, J B Lippincott Co , pp 198-204, 1936
- ⁷ Lee, J G Chronic Nonspecific Thyroiditis Arch Surg , 31, 983-1013, 1935
- ⁸ McClintock, J C, and Wright, A W ANNALS OF SURGERY, 106, 1132, 1937
- ⁹ Means, J H The Thyroid and Its Diseases Philadelphia, J B Lippincott Co , pp 499-508, 1937

BILATERAL AND BILOCULAR EMPYEMA

ADRIAN A EHLER, M D

ALBANY, N Y

AND

GEORGE N J SOMMLER, JR, M D

TRILTON, N J

FROM THE DEPARTMENT OF SURGERY OF THE UNIVERSITY OF MICHIGAN ANN ARBOR MICH

RECENT OPPORTUNITIES to care for several patients with bilateral and bilocular empyemata have stimulated our interest in these complicated forms of thoracic empyema. In order to arrive at satisfactory conclusions regarding their incidence and treatment, we have reviewed the cases of empyema at the University of Michigan Hospital from January, 1925, until August, 1938. During this period, 418 patients suffering with thoracic empyema due to pyogenic organisms occurring following respiratory infections, were admitted to the various services of the hospital. These cases do not include those with pure or secondarily infected tuberculous empyema, those in which empyema followed thoracic operations such as pulmonary lobectomy, those secondary to esophageal perforation, those following spontaneous perforation of a pulmonary abscess into the pleural cavity, or contamination of the pleura subsequent to surgical drainage of a pulmonary abscess, and those secondary to subdiaphragmatic abscess.

Of the 418 patients, 187 were classified as having chronic empyema of from several weeks' to years' duration at the time of admission. Many of these patients had had surgical or medical care elsewhere, their management at the University Hospital ranged from simple dilatation of a contracted drainage track to an extensive Schede thoracoplasty. The operative mortality rate in this group was 1.16 per cent, only two patients having died while in the hospital.

During the years covered by this study several methods of treatment were employed in the care of the 231 patients having acute empyema. All have been based, however, upon the well-understood principles of avoiding the establishment of an open pneumothorax until the lung has become fixed by pleural adhesions and of instituting early dependent drainage. Thirty-one of these patients died, giving a mortality rate of 12.4 per cent.

BILATERAL EMPYEMA

In Table I are presented the 12 cases of bilateral empyema occurring during the period of the study, an incidence of 2.9 per cent. Of these, three (Cases 2, 6 and 12) may be classified as chronic, while nine were acute at the time of admission. Four patients did not receive treatment, empyema not

BILATERAL AND BILOCULAR EMPYEMA

Volume 112
Number 3

TABLE I

BILATERAL EMPYEMA

No	Patient	Age	Sex	Interval from Onset to Adm	Etiologic Organism	Treatment	Remarks
1	C V	34	M	3 days	Unknown	None	Developed lobular pneumonia 10 days following hemorrhaphy Died 3 days later Autopsy Rt empyema 1 100 cc , Lt 700 cc Neglected case of chronic empyema admitted in bad general condition Died 4 days later in spite of transfusion and efforts to improve nutrition
2	M S	18 mos	M	4 mos	Unknown	Aspiration for 2 days Rt open drainage It closed drainage— at one operation	Admitted gravely ill Death in 2 days Autopsy Bilateral lobular pneumonia, rt empyema 300 cc , Lt 750 cc Premature infant dying of lobular pneumonia Autopsy 20 cc of pus in each pleural cavity
3	C L	14	M	2 days	<i>Streptococcus viridans</i> (blood culture)	None	Aspiration of lt empyema continued after drainage of right Rt closed drainage unsatisfactory Cured
4	R H	2 mos	M	Developed in hospital	Unknown	None	
5	M C	17	M	2 wks	Rt Type I pneumococcus Lt Type I pneumococcus	Bilateral aspiration for 10 days Rt closed intercostal drainage followed by open in 2 days It open drainage 3 wks later	
6	W S	6	M	3 mos	Rt hemolytic <i>Streptococcus</i> Lt unknown	Rt open drainage, lt operative closure of bronchopleural fistulae	Lt empyema had closed intercostal drainage elsewhere Admitted with rt empyema and lt pneumothorax with bronchopleural fistulae Lt operation after healing of rt empyema Cured
7	J S	6	F	Onset	Rt Type II pneumococcus Lt unknown	Bilateral aspiration Rt open drainage after 10 days aspiration	Diagnosed at onset Rt empyema more severe Bronchopleural fistula and 2 pockets present on rt (see Table II) Child gravely ill Cured after plastic operation for fistula
8	E Z	13	F	1 day	Rt <i>Streptococcus viridans</i>	Rt repeated aspiration, lt repeated aspiration	Admitted with rt empyema Lt developed 8 days after admission with rt already cured Cured
9	I W	9	M	Onset	Rt <i>Streptococcus viridans</i> Lt <i>Streptococcus viridans</i> and <i>Streptococcus</i>	Rt aspiration for 2 mos , lt open drainage after 4 wks aspiration Daily bilateral aspirations for 3 wks	Empyema on rt developed and aspirated 6 days after admission and just before appendectomy and drainage Had had previous conservative therapy for peritonitis Lt empyema developed 1 wk after rt Child gravely ill Cured
10	A G	18	M	Onset in hospital	Type IV pneumococcus (sputum)	None	Admitted with bilateral pneumonia Died after 20 day illness Autopsy Bilateral bronchiectasis bronchiectatic abscesses unresolved pneumonia, rt empyema, 1 500 cc , lt empyema 500 cc
11	R B	5	M	3 days	Rt Type V pneumococcus Lt unknown	Bilateral aspiration 4 wks Rt open drainage, lt continued aspiration for 3 wks	Daily bilateral aspiration for 2 wks Cured
12	R L	35	M	2 mos	Rt Type I pneumococcus Lt Type I pneumococcus	Rt open drainage, lt open drainage	Lt bronchopleural fistula Lt therefore drained first and rt 2 days later

having been diagnosed until postmortem examination, Cases 1 and 3 died after brief illnesses with bilateral lobular pneumonia, Case 4 is that of a premature infant dying of malnutrition and pneumonia, with very small amounts of pus in both pleural cavities, Case 10 was admitted with a tentative diagnosis of bilateral lobular pneumonia and was apparently recovering until a sudden change in his condition occurred two days before his death, the postmortem examination demonstrated bronchiectasis, bronchiectatic abscesses, and bilateral empyema

Of the eight treated patients with bilateral empyema, one was cured by bilateral aspiration. Three patients were treated with aspiration alone on one side and with open drainage, following aspiration, on the contralateral side. Aspiration followed by bilateral drainage was employed for one patient, three weeks intervening between the drainage operations. Prolonged aspiration was deemed unnecessary for Case 12 in view of its chronic nature, the two sides were drained two days apart following diagnostic taps. The one patient who died was an 18 month old child, admitted with bilateral empyemata of four months' duration, and in extremely poor general condition. Following aspiration for two days, in order to diminish the amount of thick pus in the hemithoraces, both sides were drained by an efficient air-tight technic at one operation, the child died four days later of advanced malnutrition in spite of transfusions and other efforts to improve his condition. Case 6 presented an interesting condition, on admission, a right-sided empyema was present, while on the left side there was an apparently uninfected pneumothorax with multiple bronchopleural fistulae, which had developed following drainage of a left-sided empyema elsewhere, the drainage tract was healed. Cure of the right-sided empyema followed drainage, after complete healing of the right-sided empyema a left thoracotomy was performed with suture of the fistulae and air-tight closure of the thoracic wall without drainage, the left lung slowly reexpanded and complete recovery ensued.

The operative mortality in the eight treated cases was 12.5 per cent. This is a lower percentage than we have been able to find in any other group comprising more than one or two cases reported in the literature, with one exception. The mortality rate of treated bilateral empyema is almost exactly that of the entire group of acute empyema cases in the University Hospital. In reviewing the methods of treatment employed in our cases, it is noticeable that for acute empyemata aspiration was persisted in for a much longer period than the average time. Furthermore, of the 16 empyemata in eight patients, five were cured by aspiration alone, this is a proportionately greater number than in the unilateral group. In no case, it should be noted, did cardiac or respiratory symptoms follow open drainage with the institution of efficient air-tight drainage.

ILLUSTRATIVE CASE REPORT

Case Report—Bilateral Empyema. R. L. (Case 12, Table I, Figs 1 to 4), male, age 33, was admitted to the University Hospital, July 8, 1938. Eight weeks previously he

BILATERAL AND BILOCULAR EMPYEMA

had developed bilateral empyema secondary to lobular pneumonia, his physician had performed numerous thoracenteses. After four weeks, persistent cough became productive of large amounts of purulent sputum. On admission, the patient was feeble and quite debilitated, his sputum was purulent and moderate in amount. Physical examination and roentgenologic studies demonstrated pleural effusions in both hemithoraces posteriorly, the presence of a definite fluid level on the left side, and the purulent sputum suggested the presence of a bronchopleural fistula. Bilateral thoracenteses demonstrated pus, in which cocci were found on smear, and from which Type I pneumococci were cultured.

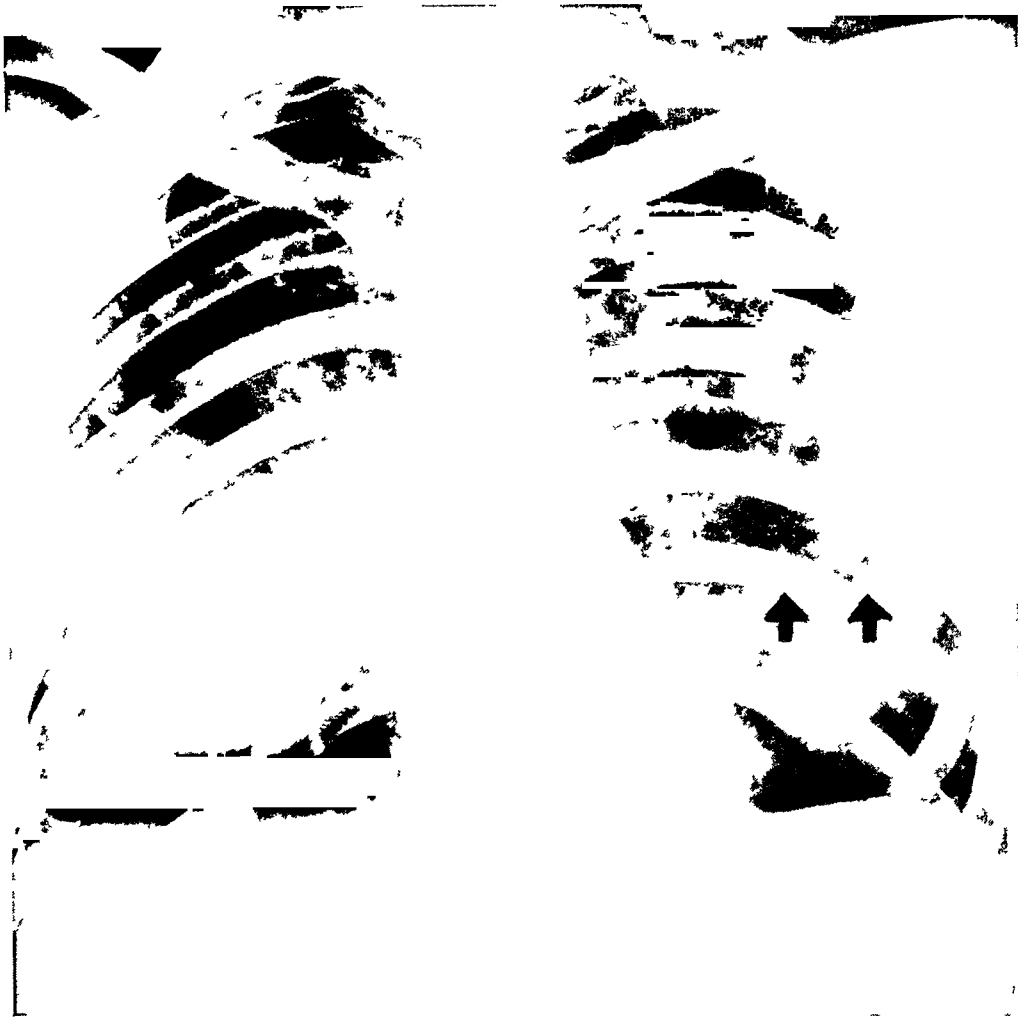


FIG 1—Case 12, Table I. Postero-anterior roentgenogram demonstrating bilateral pleural effusion with fluid level on left side.

Because of the probable left-sided bronchopleural fistula, the left empyema was drained first on the day of admission. Closed, dependent drainage was instituted following the resection of a portion of the eighth rib in the midscapular line, under local anesthesia. On July 10, two days later, the empyema on the right side was dependently drained, with the resection of a portion of the ninth rib in the midscapular line, closed drainage was established. Since both tubes had necessarily been placed in the posterior portion of the chest, drainage was cut off by the patient lying on his back. Closed drainage was, therefore, abandoned, and the tubes were cut off just external to the skin. This was safe in view of the chronicity of the empyemata and the probable fixation of the lungs and mediastinum. The patient made an uneventful recovery with complete obliteration of the empyemata.

In 1903, Hellin¹ collected the reports of 114 cases of bilateral empyema. The mortality rate was 30.1 per cent, which he considered too low to be representative in view of the tendency to communicate only with successfully treated single and series of cases. He estimated that bilateral pleural involvement occurs in 7.7 per cent of all empyemata. Keyes² found 38 cases in the



FIG. 2.—Case 12, Table I. Right lateral roentgenogram demonstrating that both empyemata lie posteriorly. The left empyema with fluid level is obscured by the right.

literature from 1910 to 1930, and added three treated at the New York Hospital. During the exceptionally grave influenza epidemics of 1917-1918, Stevens³ noted that 29.64 per cent of patients with bilateral pneumonia also suffered with empyema, in 40 per cent the pleural disease was unilateral and in 60 per cent bilateral. Unilateral *Streptococcus* empyema resulted in a mortality rate of 42.2 per cent and bilateral of 89.1 per cent, bilateral pneumococcus lobar pneumonia resulted in a mortality rate of 21.6 per cent when associated with unilateral empyema, and of 78.3 per cent with bilateral empyema, the

bilateral *Staphylococcus* pneumonia-empyema was almost invariably fatal. Dunham⁴ reported 536 autopsies of patients dying of empyema during the 1917-1918 epidemics, of this group, 245, or 45.7 per cent, had bilateral empyema. Maes, Veal and McFetridge⁵ found, however, only one instance of



FIG. 3—Case 12, Table I. Postero-anterior roentgenogram taken 31 days following drainage of the empyema on the left side, and 29 days after the drainage of that on the right side, iodized oil has been injected into the sinuses.

bilateral involvement among 100 fatal cases of empyema at the Charity Hospital of Louisiana.

We have endeavored to determine the incidence of bilateral empyema by gathering statistics from a number of articles on empyema published since 1921. Reports of single or several isolated cases have been disregarded since they do not furnish reliable information with regard to incidence.

The articles by Ladd and Cutler,⁶ Brown,⁷ Farr and Levine,⁸ Ravnitsky and Bogin,⁹ Ochsner and Gage,¹⁰ Keyes,² Locke,¹¹ Bauer,¹² Cohen,¹³ Rentschler,¹⁴ Steinke,¹⁵ Harloe,¹⁶ Bohrer,¹⁷ Michalowicz,¹⁸ Steinke,¹⁹ Burpee,²⁰ Utter,²¹ and Schmidt²² report 5,664 cases of empyema, of which 101 were bilateral, an incidence of 1.8 per cent. The articles by Beyer,²³ Peck and Cave,²⁴ Rienhoff and Davison,²⁵ Foster,²⁶ Hudson,²⁷ Muller,²⁸ Jamin,²⁹ Danna,³⁰ Graham and Beck,³¹ Brann,³² Kalges,³³ McEachern,³⁴ Carlson and



FIG 4—Case 12 Table I Photograph of the patient showing the drainage sites

Bowers,³⁵ Tanner,³⁶ Mason,³⁷ Penberthy and Benson,³⁸ and Niemeier³⁹ list an additional 2,155 cases in series not containing any bilateral case. The incidence of bilateral empyema in the entire group of 7,819 cases is 1.3 per cent.

The results of treatment in the large groups of patients with bilateral empyema are interesting. Ochsner and Gage¹⁰ reported five cases without a death, but did not mention the exact mode of treatment. Seven of Locke's¹¹ 11 patients with bilateral empyema died, two of Harloe's¹⁶ eight, one of Bohrer's¹⁷ six, 25 of Michalowicz's¹⁸ 28, and all of Steinke's¹⁹ 11. Aside from the results of Ochsner and Gage,¹⁰ the best results published prior to our series are those of Bohrer,¹⁷ with a mortality rate of 17 per cent, and of Harloe,¹⁶ with 25 per cent. These authors treated their bilateral cases with closed intercostal drainage. Bohrer¹⁷ performed the bilateral operations one

or two days apart, while Harloe¹⁶ drained both sides at the same operation, similar drainage was used for their unilateral cases

BILOCULAR EMPYEMA

Among the 418 patients with empyema were 13 with bilocular pockets in the same pleural cavity giving an incidence of 3.1 per cent. Of the 13 cases, one was admitted following drainage elsewhere, one developed in the hospital, one was of three weeks' duration on admission, one of one month's,

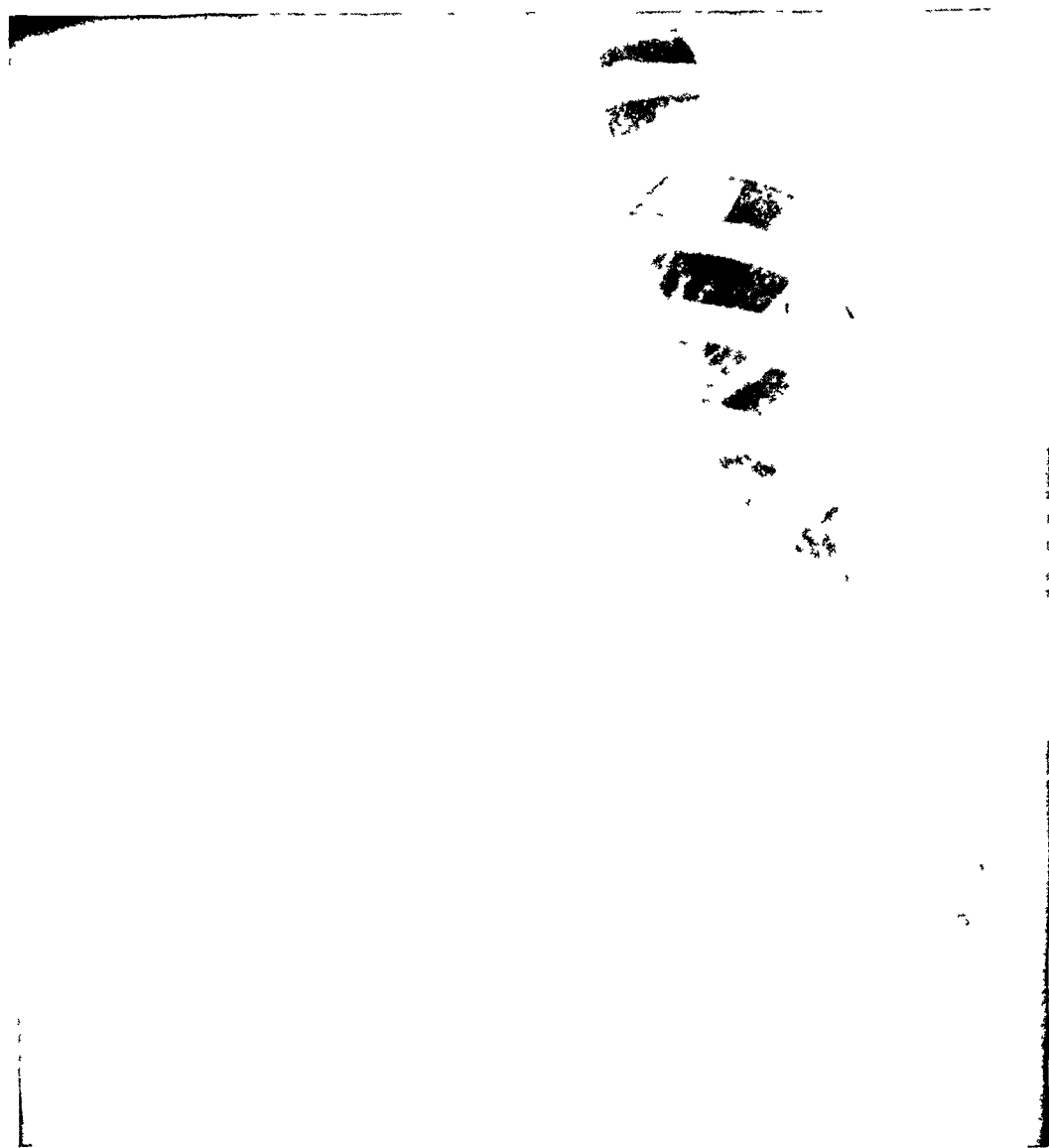


FIG 5—Case 12, Table II. Postero-anterior roentgenogram, taken on admission to hospital, demonstrating the right pleural effusion.

three of six weeks', five of four months', and one of 14 months', it should be noted that only three may be considered early cases. In two cases (Cases 3 and 11), the pockets were widely separated at the base and apex, and the diagnosis was made preoperatively. In Case 9, which was admitted with a draining wound, the diagnosis of an undrained pocket was apparent before the second operation. In three cases (Cases 4, 5 and 6), the bilocular condi-

tion was discovered at the time of operation, when both pockets were drained, in Case 6, previous closed intercostal drainage had been instituted one month prior to open operation, with rib resection. In the remaining seven cases, the diagnosis of a second, undrained pocket was made from five days to three months following initial operation. In only five cases, including the three in which the diagnosis was made during the course of operation, was it possible



FIG 6—Case 12 Table II. Right lateral roentgenogram taken following aspiration of pus and injection of air before transfer to the Thoracic Service. Anterior and posterior fluid levels are clearly visible.

to institute double drainage through a single operative wound, in the remaining eight cases two incisions were needed.

Only two patients died. The cause of death in Case 9 was multiple actinomycotic liver abscesses, the patient dying after closure of the empyema, which was probably caused by the same organism. Case 6 died of osteomyelitis of the ilium, which developed while his empyema was draining, the osteomyelitis probably being metastatic, it is possible that earlier recognition and drainage of the second empyema pocket might have effected an earlier

TABLE II

BILOCULAR EMPYEMA

No	Patient	Age	Sex	Dura- tion	Etiologic Organism	Means of Diagnosis	Treatment	Remarks
1	C E 239773	5	M	3 mos	Type II pneumococcus	Postoperative x-ray	Drainage of second pocket through first incision, 5 days later	Continued fever led to study Cured
2	E K 307912	7	F	6 wks	Type I pneumococcus and <i>Streptococcus</i>	Postoperative x-ray	Separate drainage of 2 pockets 1-mo interval	Diagnosis of bilocular empyema suspected on admis- sion Symptoms recurred after first drainage Cured
3	F S 334462	20	M	4 mos	Type I pneumococcus and <i>Streptococcus haemolyticus</i>	Preoperative x-ray	Separate drainage of 2 pockets with 2 separate incisions 4- day interval	Superior and inferior pockets well separated Cured
4	T Q 336130	30	F	6 wks	Type I pneumococcus	At operation	Both drained through one inci- sion	Cured
5	J S 341343	6	F	Onset	Type II pneumococcus	At operation	Second pocket opened at opera- tion through same wound	Bilateral empyema (see Table I) Biloculation sus- pected by x-ray Bronchopleural fistula closed later by plastic operation Cured
6	R H 343608	20	M	4 mos	<i>Streptococcus nonhaemolyticus</i>	At operation	At open drainage 1 mo after closed intercostal drainage sec- ond pocket found and drained Later redrainage necessary	Empyema cured In meantime, developed a metastatic osteomyelitis of ilium causing death 1 yr after first admission
7	A J 375500	5	F	1 mo	Type I pneumococcus	Postoperative x-ray	Separate drainage of 2 pockets 7-wk interval	Second pocket required redrainage Lay superiorly Cured
8	F S 384530	4	M	6 wks	<i>Streptococcus nonhaemolyticus</i>	Postoperative x-ray	Separate drainage of 2 pockets 6-wk interval	Persistent recurrent symptoms led to study Cured
9	C N 388287	53	M	3 mos	No growth on cultures Actinomycosis?	Preoperative x-ray	Admitted with drained empy- ema and large undrained ante- rior pocket Drained through old wound	Died 5 mos later of multiple actinomycotic liver ab- scesses that had been in part drained
10	D L 410550	17	F	4 mos	(1) <i>Streptococcus haemolyticus</i> (2) As above with <i>B. coli</i>	Postoperative x-ray	Separate drainage of 2 pockets 4-wk interval	Persistent symptoms Second pocket anterior Schede thoracoplasty later for posterior pocket Cured
11	L C 411210	52	F	4 mos	Type III pneumococcus in both	Preoperative x-ray	Separate drainage of 2 pockets 2 day interval	Widely separated anterior-superior and posterior-inf- rior pockets Cured
12	D K 415544	16	F	3 wks	Type V pneumococcus	Postoperative x-ray	Separate drainage of 2 pockets 8 day interval	Persistent symptoms followed first drainage Cured
13	W B 416265	27	M	4 mos	(1) Anaerobic <i>Streptococcus</i> <i>haemolyticus</i> (2) <i>Strepto-</i> <i>coccus viridans</i>	Aspiration	Separate drainage of 2 pockets 3 mo interval	Returned to hospital after closure of first pocket Re- current symptoms found due to small lateral pocket originally interpreted in roentgenogram as thickened pleura Cured

cure of the empyema and prevented the metastatic infection. The mortality rate for the series of 13 cases of bilocular empyema is 15 per cent, if the patient who died of hepatic actinomycosis is eliminated, the rate is 8.3 per cent.

The only instance of an empyema with more than two separate pockets treated at the University Hospital occurred in a male, age 23, who was ad-



FIG 7—Case 12, Table II. Right lateral roentgenogram taken 45 days following drainage of the posterior pocket and 37 days following the anterior, iodized oil has been injected into the sinuses.

mitted with a subphrenic abscess which was later drained. Three distinct empyema pockets were drained, as recognized, with separate rib resections, before the patient was discharged, apparently well. Various organisms of the pyogenic group were cultured, as well as *Actinomyces*.

ILLUSTRATIVE CASE REPORT

Case Report—Bilocal empyema. E. K. (Case 12, Table II, Figs 5 to 8), female, age 16, was admitted, January 4, 1938. A diagnosis of postpneumonic empyema had been

made ten days previously. Physical examination and roentgenologic studies demonstrated a large effusion in the right chest. Daily thoracenteses were performed for five days, with replacement of air on several occasions, Type V pneumococcus was cultured from the aspirated pus.

After transfer to the Section of Thoracic Surgery on January 10, a portion of the tenth rib was resected with the institution of closed air-tight drainage. The surgeon believed that all the empyema pus had been drained. The patient's temperature remained elevated, however, and a comparison of the preoperative and postoperative roentgenograms disclosed an anterior undrained pocket, which was especially well demonstrated in the lateral view. On January 18, a segment of the fifth rib was removed through a submammary incision with the removal of 180 cc of pus from the pocket, closed drainage was employed. Both pockets became completely obliterated.

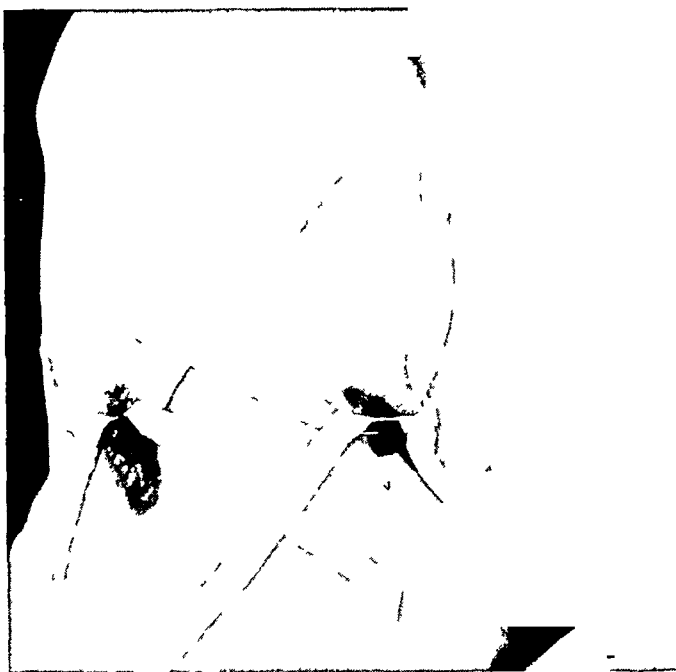


FIG 8—Case 12, Table II. Photograph of the patient showing the drainage sites.

Van Allen⁴⁰ treated one patient with three empyema pockets in one pleural cavity, which arose, he believed, from separate bronchopneumonic foci, they were drained by separate incisions made as each pocket was discovered during a 15-day period. Lilienthal⁴¹ drained five separate pockets at one operation, three distinct organisms were cultured. Mason³⁷ reported the drainage of three pockets through two incisions. Of 351 cases of acute empyema reported by Harloe,¹⁶ 22.7 per cent were multilocular. Danna,³⁰ in treating 75 cases of acute empyema with aspiration and air replacement, found three with multiple loculations, one of which had three pockets in the same pleural cavity.

SUMMARY AND CONCLUSIONS

In a large collected group of empyema cases, the incidence of bilateral empyema was 1.3 per cent, in our own series of 418 cases, it was 2.9 per cent. The operative mortality in eight treated cases was 12.5 per cent, which is almost identical with that of acute empyema in the same hospital. The good

results obtained from treatment resulted, we believe, from the meticulous care taken in these cases to observe the proper principles of therapy

Loculation of pus in two places in the same pleural cavity occurred in 13 of our patients, an incidence of 31 per cent. Loculation occurred chiefly in chronic empyema. Recognition of multiple loculation depends upon careful study of preoperative and postoperative postero-anterior and lateral or oblique roentgenograms whenever the condition is suspected from clinical and physical findings. The foci should be drained as they are recognized, either through the original or supplementary incisions.

BIBLIOGRAPHY

- ¹ Hellin, Dionys. Das doppelseitige Empyem. Berl klin Wchnschr, 3, 1415, 1905
- ² Keyes, E. L. Bilateral Empyema of the Pleural Cavities. ANNALS OF SURGERY, 93, 1050, 1931
- ³ Stevens, F. A. Clinical Aspects of Streptococcus Pneumonia-Empyema. Medical Department of the United States Army in the World War, 11, Surgery, 261. Government Printing Office, 1922
- ⁴ Dunham, E. K. Pathology. Medical Department of the United States Army in the World War, 11, Surgery, 142, Government Printing Office, 1922
- ⁵ Maes, U., Vcal, J. R., and McFetridge, E. M. The Mortality of Empyema. An Analysis of 100 Consecutive Deaths from the Records of the Charity Hospital in New Orleans. Jour Thor Surg, 4, 615, 1935
- ⁶ Ladd, W. E., and Cutler, G. D. Empyema in Children. Am Jour Dis Child, 21, 546, 1921
- ⁷ Brown, H. P., Jr. Empyema Thoracis. An Analysis of 250 Cases Treated at Children's Hospital of Philadelphia. ANNALS OF SURGERY, 77, 401, 1923
- ⁸ Farl, C. E., and Levine, M. T. Empyema in Children. Surg, Gynec and Obstet, 46, 79, 1928
- ⁹ Ravnitsky, N., and Bogin, M. The Treatment of Empyema in Children. Long Island Med Jour, 24, 194, 1930
- ¹⁰ Ochsner, A., and Gage, I. M. Treatment of Acute Empyema Thoracis with a Review of 100 Consecutive Cases. Proc Interstate Postgrad Med Assembly N. A., 6, 261, 1930
- ¹¹ Locke, E. A. Acute Empyema. New Eng Jour Med, 203, 391, 1930
- ¹² Bauer, C. Über Behandlung und Komplikationen der Pleuraempyeme. Arch f klin Chir, 168, 269, 1931
- ¹³ Cohen, M. Acute Suppurative Pleurisy. A Study of 123 Cases. Surg, Gynec and Obstet, 54, 696, 1932
- ¹⁴ Rentschler, C. B. Acute Empyema of Thorax. ANNALS OF SURGERY, 96, 987, 1932
- ¹⁵ Steinke, C. R. Bilateral Empyema. Jour Thor Surg, 2, 287, 1933
- ¹⁶ Harloe, R. F. Empyema. Am Jour Surg, 26, 231, 1934
- ¹⁷ Bohrer, J. V. Acute Empyema in Children. ANNALS OF SURGERY, 100, 113, 1934
- ¹⁸ Michalowicz, M. 1,450 cas de pleurise purulente chez enfants. Rev fran de pediatrie, 12, 545, 1935
- ¹⁹ Steinke, C. R. Acute Empyema in Children. ANNALS OF SURGERY, 101, 617, 1935
- ²⁰ Burpee, C. M. Acute Empyema in Infancy and Childhood. A Statistical Study with a Comparison of White and Colored. Arch Ped, 53, 449, 1936
- ²¹ Utter, O. Über die Behandlung und Prognose der Pleuraempyeme in Kindesalt. Acta chir Scandinav, 78, 545, 1936
- ²² Schmidt, A. Beobachtungen über 135 Fälle von Thoraxempyeme bei Kindern. Med Klin, 32, 937, 1936

- ²³ Beye, H L Analysis of 100 Cases of Empyema in Relation to Treatment Minne-
sota Med , 6, 401, 1923
- ²⁴ Peck, C H and Cave, H W Acute Suppurative Pleurisy Surg , Gynec and
Obstet , 36, 357, 1923
- ²⁵ Rienhoff, W F, Jr, and Davison, W C Empyema in Infants under Two Years
of Age Arch Surg , 17, 676, 1928
- ²⁶ Foster, L C Treatment of Acute Empyema Thoracis , with Report of 153 Consecu-
tive Cases ANNALS OF SURGERY, 92, 212, 1930
- ²⁷ Hudson, H W, Jr Treatment of Acute Empyema Thoracis , 86 Cases New Eng
Jour Med , 202, 853, 1930
- ²⁸ Muller, G P The Mortality of Operations for Acute Empyema Jour Thor Surg ,
1, 15, 1931
- ²⁹ Jamin, F Ueber die Behandlung des Pleuraempyeme bei Kindern Deutsch Ztsch
f Chir , 229, 164, 1930
- ³⁰ Danna, J H Some Principles Involved in the Pathology and Treatment of Empyema
Thoracis Surg , Gynec and Obstet , 56, 294, 1933
- ³¹ Graham, E A , and Berck, M Principles Versus Details in the Treatment of Em-
pyema Thoracis ANNALS OF SURGERY, 98, 530, 1933
- ³² Biann, R Zur Behandlung der Pleuraempyeme im Kindesalter Monatsch f Kinder ,
57, 326, 1933
- ³³ Kalges, F Ergebnisse der Behandlung des kindlichen Pleuraempyeme mittels Rip-
penresection und geschlossener Drainage Zentralbl f Chir , 60, 627, 1933
- ³⁴ McEachern, J B The Treatment of Acute Empyema in Infancy and Childhood
Brit Jour Surg , 20, 653, 1933
- ³⁵ Carlson, H A , and Bowers, W F Acute Empyema Mortality, Healing and
Methods of Treatment Internat Surg Digest, 18, 131, 1934
- ³⁶ Tanner, E K Suppurative Pleurisy Am Jour Surg , 26, 248, 1934
- ³⁷ Mason, J M Empyema in Children South Med Jour , 28, 219, 1935
- ³⁸ Penberthy, G C , and Benson, C D A Ten-Year Study of Empyema in Children
ANNALS OF SURGERY, 104, 579, 1936
- ³⁹ Niemeier, O W The Treatment of Empyema Thoracis Canad Med Assoc Jour ,
35, 172, 1936
- ⁴⁰ Van Allen, C M Empyema with Multiple Foci Surg Clin North Amer , 9, 407,
1929
- ⁴¹ Lilienthal, H A In Discussion of Fair, C E , and Levine, M T S

THE TREATMENT OF PERIANAL TUBERCULOSIS

EMIL GRANET, M D

NEW YORK, N Y

FROM THE SURGICAL SERVICE, WEA VIEW HOSPITAL, STATEN ISLAND, N Y

SIXTY YEARS AGO, regarding operation in this condition, Allingham¹ wrote "I should say from my experience, if you have a phthisical patient suffering from a fistula which gives him much pain or inconvenience, by taking certain precautions you may relieve him of it without running any risk of damaging him" In recent years excellent results have been reported following radical excision of perianal infections in patients with active pulmonary tuberculosis Martin,² at the Chicago Municipal Sanatorium, reported 87 per cent cures in 75 cases, Berry,³ at Bellevue Hospital, had 72 per cent cures in 18 cases, and Chisholm,⁴ in Denver, cured 98 per cent of 71 patients

Unfortunately, however, the erroneous and outmoded concept that perianal tuberculous infections should be treated conservatively has survived The belief is widely held that these conditions in patients with pulmonary tuberculosis, when operated upon, are apt to recur, that the lung disease may be reactivated or made worse This conservative attitude is deeply entrenched in the minds of internists as shown by answers of 28 Colorado phthisiologists to a questionnaire as to operative treatment of perianal infections in tuberculous patients (Table I)

TABLE I

PERIANAL INFECTIONS IN PATIENTS WITH PULMONARY TUBERCULOSIS

All More Than 70 Per Cent Positive Biopsy for Tuberculosis

Name of Author	No of Cases	Cures
Martin ² (Chicago)	75	71 (87%)
Berry ³ (Bellevue, N Y)	18	14 (72%)
Chisholm ⁴ (Denver)	71	70 (98%)

DO YOU RECOMMEND OPERATION?

Chisholm's⁴ Questionnaire to 28 Colorado Physicians

Yes	2
No	22
Selected Cases	4

My interest in this problem was stimulated some years ago by the apparent disinterest in the management of perianal infections occurring in tuberculous patients in one of our large municipal hospitals Surgery consisted in conservatively incising abscesses and merely opening fistulae, with the result that few patients were cured or definitely improved Patients with wide-

spread perianal abscesses and multiple fistulae were considered inoperable, with the result that they continued a miserable existence, many of them veritably lying in a bed of tuberculous pus. Noxious effects resulting from the presence of pus in these patients were manifested by systemic reactions such as fever, anorexia, weight loss and amyloidosis. Pain depended upon the severity of the inflammatory reaction and anatomic distribution of the lesions.

The despondence of these patients was graphically described by Allingham¹ as follows: "There is a circumstance which occasions me sometimes to interfere in a case of fistula in phthisical patients, and that is, the mental depression which the rectal affection creates. Frequently the sufferer thinks much more about his fistula than he does about what he calls 'his little cough,' and is quite dismayed and brought to despair when you tell him that you cannot do anything to cure him. I am certain that few things conduce more to the rapid progress of phthisis than mental anxiety and loss of hope."

A Proctologic Service was instituted at the Sea View Hospital for Tuberculosis in 1935, primarily to study methods of management of these extensive perianal tuberculous lesions. Table II demonstrates that many active perianal infections were present in patients at Sea View, and that individuals so afflicted readily accept surgery when offered a chance for cure.

TABLE II
OPERATIONS FOR PERIANAL INFECTIONS AT SEA VIEW HOSPITAL
Abscesses, Fistulae or Both

1928 through 1931	1
1932 through 1934	14
<i>Proctological Service Instituted April, 1935</i>	
1935	14
1936	23
1937	25
1938	29

Perianal infections are frequent in patients with pulmonary tuberculosis. Walsh reported perianal abscesses or fistulae found at autopsy in 9 per cent of a series of patients dead of phthisis. Frequency of perianal infections complicating pulmonary tuberculosis varied from 5 per cent, reported by Chisholm, of Denver, to 11.7 per cent reported by Maimo,⁵ of Brooklyn, in a carefully studied group of 357 tuberculous patients at the Kingston Avenue Hospital.

In the general nontuberculous population, anorectal infections occur in 0.5 to 0.6 per cent (Table III). From these statistics, it is reasonable to conclude that tuberculous perianal lesions probably originate, in most instances, through contact infection with tubercle bacilli in the stools of phthisic patients. The mechanism of infection, I believe, depends on the clinical type

of perianal lesion present Commonly seen are Perianal abscess (A) discrete—circumscribed, (B) seipiginous—subcutaneous Fistula or sinus Tuberculous anal fissure or ulcer Lupus of the anus Tuberculid

TABLE III
INCIDENCE OF CHRONIC PERIANAL INFECTION

<i>Sinuses, Fistulae, Abscesses</i>		
Pulmonary Tuberculosis Hospitals		
Martin, ²	Chicago Municipal Sanatorium	7 0 %
Chisholm, ⁴	Denver, Jewish National San	5 0 %
Marino, ⁶	Brooklyn, Kingston Avenue	11 7 %
General Hospitals		
Leslie, ³	Vancouver General Hospital	0 52 %
Leslie, ³	Massachusetts General	0 6 %
Marino, ⁶	Brooklyn Hospital	0 6 %

Pathology—Acute, discrete abscess probably starts as a pyogenic cryptitis at the level of the anorectal line Edema of the adjacent papilla seals the anal opening of the crypt and so prevents drainage into the rectum Inflammatory exudate burrows through the sphincter muscles and perianal fat to point eventually as a perianal abscess It is likely that because of their acute onset, most lesions of this type are primarily pyogenic in origin Many of them are secondarily infected with tubercle bacilli, thereby becoming contact infections after the abscess ruptures spontaneously or is inadequately drained by incision

Seipiginous subcutaneous abscesses were more common in our series The lesion characteristically appears as a widespread chronic subcutaneous induration consisting largely of tuberculous granulation tissue with little pus, the overlying edematous skin colored a livid dusky red Pathogenesis in these cases consists of a direct spread of contiguous tubercles along the perianal lymphatic network, recently demonstrated by Nesselrod⁶ This lymphatic network completely circumscribes the anus to empty into collecting vessels running toward the inguinal nodes Tubercle bacilli from swallowed sputum enter the lymphatics through a break in the epithelium of the anal canal The infection spreads along the perianal lymphatic network, often extending toward the groin along the course of the collecting lymphatics (Fig 1) In our series all patients with seipiginous subcutaneous lesions had positive biopsies for tuberculous granulation tissue

Perianal fistulae occurring in tuberculous patients usually result from previous abscesses They have at least one external opening on the skin as well as an internal orifice leading into the rectum or anus Sinuses similarly result from abscesses but differ from fistulae in having but one orifice, either internal leading into the gut, or external opening through the skin Even in tuberculous individuals these tracts are occasionally pyogenic, providing, however, that the original abscess was nontuberculous A simple

pyogenic fistula or sinus may become tuberculous by contamination following prolonged contact with tubercle-laden feces. A tuberculous fistula, characteristically, is seen as an irregularly serrated orifice, widely patulous, surrounded by edematous, inflamed, undermined skin of a livid color (Fig 2)

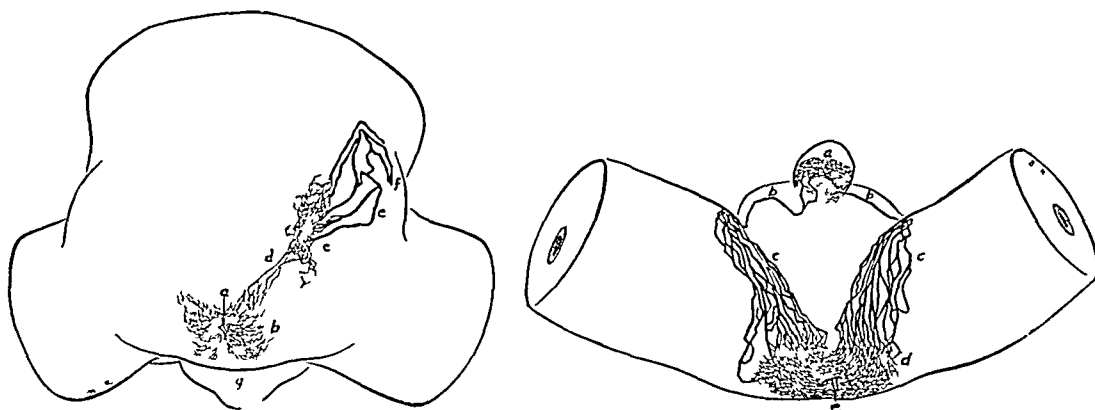


FIG 1—Injection of perianal lymphatics of the anal margin. (Left) Perianal and gluteal lymphatics (posterior view) of a male, white fetus at term. Injections made along the anal margin and in the skin over the gluteal region, using mercury. (a) Anus. (b) Network of the perianal skin. (c) Plexus of the skin over the gluteal region. (d) Anastomotic vessels. (e) Collecting vessels. (f) Collecting vessels from the superior gluteal region passing to the groin. (a) Scrotum. (Right) Penile and perianal lymphatics viewed from below in the same specimen as that represented in Figure 1 left. Injections made in the skin of the shaft, using mercury. (a) Network of the skin of the shaft of the penis. (b) Collecting vessels from the network of the shaft. (c) Collecting vessels from the perianal network. (d) Network of the perianal skin. (e) Anus. (Nesselrod, J. P. *ANNALS OF SURGERY*, 104, 908, Fig 1, November, 1936)

Chronic anal fissures in tuberculous patients with positive sputa frequently become contaminated with tubercle bacilli and become tuberculous ulcers. Clinically they appear as anal ulcers, the edges of which are elevated and indurated with dark, violaceous, inflamed epithelial tissue (Fig 3)



FIG 2—External opening of a typical tuberculous fistula



FIG 3—Tuberculous infiltration of a chronic anal fissure

Lupus or tuberculosis of the perianal skin is seen most frequently in terminal toxic patients in the advanced age group. Our cases were considered inoperable mainly because of extensive destruction of perianal skin and sphincter muscle. Solitary tubercles are rare and when occurring in the

perianal region are generally regarded as metastatic tubercles. They should be excised.

Diagnosis of Perianal Tuberculosis—Inasmuch as at least 5 per cent of patients with pulmonary tuberculosis have perianal infections as contrasted against 0.5 per cent of the nontuberculous population (Table III), it follows that perianal infections occur ten times more frequently in tuberculous than in nontuberculous people. In patients with pulmonary tuberculosis, therefore, it is reasonable to expect that most of these perianal infections are tuberculous. Their etiology is dependent on the presence in the feces of tubercle bacilli originally swallowed as tubercle-laden sputum.

In this series, diagnosis of tuberculous perianal infection was based upon the examination of biopsy material obtained at operation showing histopathologic evidence of tuberculous granulation tissue, *i.e.*, typical tubercle formation with central necrosis, fibroblastic capsule, monocytic infiltration and giant cells. Sweany⁷ points out that failure of histopathologic diagnosis in tuberculous perianal lesions depends upon the fact that typical changes are present only in "live granulations." In the taking of specimens, the surgeon should attempt removal of areas of tract containing "live granulations" intact. Often the character of the fistula or abscess affords no granulation tissue. Necrosis, overgrowth of secondary pyogenic invaders with subsequent slough of granulations and fibrosis all tend to change the pathologic characteristics of the original granulation tissue so that even the most experienced pathologist could not venture a diagnosis of tuberculosis. Sweany concludes that "with careful, repeated, or complete samplings, with serial sections and with careful study, over 75 per cent of fistulae and abscesses in tuberculous patients should be found tuberculous. No doubt, all but an insignificant minority are tuberculous."

Recognition of tuberculous perianal lesions by their gross characteristics at operation is, in my opinion, extremely important in attaining even partial cure. The majority of our patients at the time of operation, had multiple lesions. These consisted of acute or chronic circumscribed abscesses, chronic, diffuse, serpiginous subcutaneous abscesses with fistulae or sinuses. At the margins, or in the depths of the lesion, typical tuberculous granulation tissue was seen. This appeared livid, cyanotic and almost violaceous in color, it was friable, and characterized by absence of free bleeding when wiped away. In patients with subcutaneous serpiginous infection, the tuberculous granulation tissue followed the perianal lymphatic network, frequently extending widely in all directions.

Anesthesia—Internists have objected to operation in this condition because of the possibility of reactivating the primary disease in the lungs. This was undoubtedly so previously, when ether was employed, with the resultant probability of disseminating tubercle-laden sputum by aspiration into an uninvolved lung region. Local infiltration anesthesia is contraindicated, because of the possibility of disseminating existing infection with the anesthetic solu-

tion Caudal and parasacral block is the procedure of choice on our service. Systemic reactions are minimal, and anesthesia complete. The usual technic is employed, namely, 30 cc of a 2 per cent procaine solution is injected into the epidural canal, and 10 cc into the second and third sacral foramina on each side. Low spinal anesthesia was employed in a few patients in whom the sacral canal could not be entered. Fifty milligrams of neocaine was the dose required to insure good anesthesia. Premedication consisted of 0.2 Gm of phenobarbital, two hours before operation.

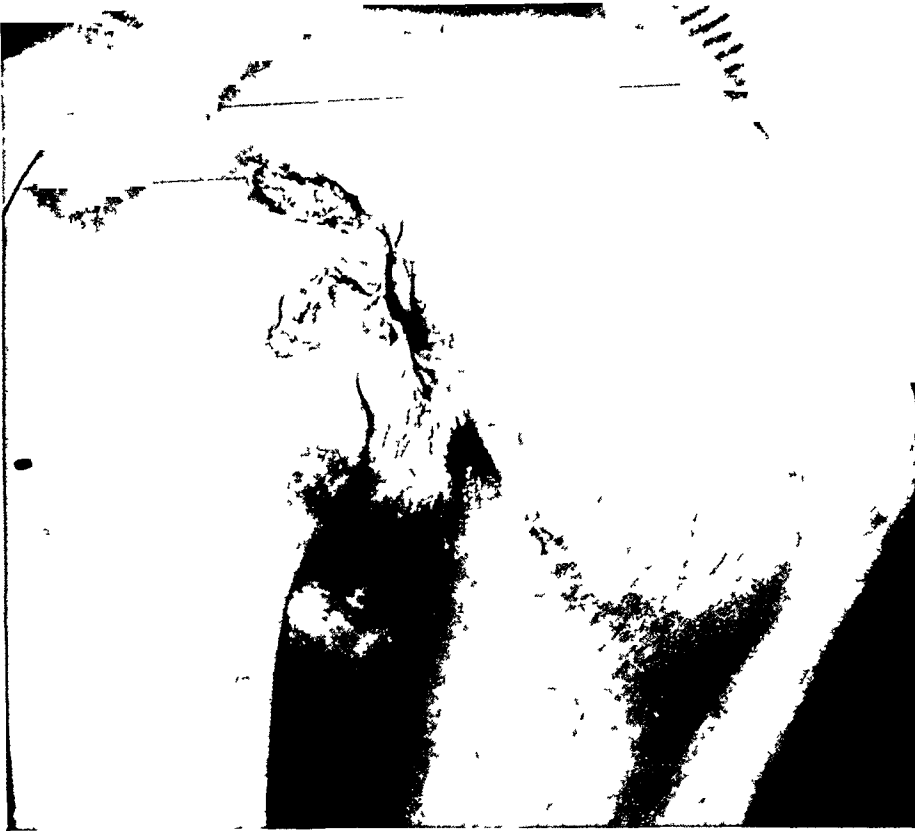


FIG. 4—Extensive serpiginous subcutaneous abscess with extension along the inguinal lymphatics. Three weeks after the third stage, showing bilateral inguinal lesions (second stage) almost healed and a bridge of intact skin between the two excised abscess cavities.

Treatment—The exact procedure used in treating perianal tuberculosis, of necessity, depends on the individual lesion. To cure perianal tuberculous infection, radical excision of the entire pathology is essential. Conservative surgical measures are futile except in individual patients in the terminal stage of pulmonary tuberculosis. The failure of conservative incision is shown by the fact that 35 per cent of the patients in our series had been previously operated upon in other hospitals, with failure of cure even after several years.

As stated, effective operative treatment demands the excision of all perianal tuberculous tissue. Chronic tuberculous lesions tend to extend widely around the anus with multiple fistulous tracts, often with the internal orifice proximal to the internal sphincter muscle. In such cases, good surgical judgment would counsel operation in multiple stages, in order to insure gradual

replacement of excised tissues with blocks of fibrous scar tissue so as to preserve support of the perineal floor. Any uninvolved skin and subcutaneous fat between fistulous or abscessed areas must be saved, as these islands of normal tissue tend to maintain elasticity and minimize distortion due to scar contracture (Fig 4).

When the internal opening of the fistulous tract enters the rectum through or above the internal sphincter, operation is necessarily performed in multiple stages. The infected perianal lesion is excised widely down to the sphincter but the tract leading through or above the sphincter muscle is left intact. A seton in the form of heavy silk tape, is passed through the remaining fistula and tied so as to encircle the sphincter muscles. This simplifies identification of the fistula at the time of the secondary revision. The



FIG 5—(A) Wound after excision of the chronic circumscribed abscess with internal opening of the sinus distal to internal sphincter. (B) Healed scar after eight weeks.

primary wound heals by granulation, so that eventually a wide, gaping perianal wound is replaced by a block of firm fibrous scar tissue adherent, in the anal portion, to the lateral borders of the sphincter muscles. When this has occurred, using the seton as a lead, a grooved director is passed through the remaining fistulous tract and presented externally from the anus at right angles to the direction of the sphincter muscle fibers. The muscle is divided on the grooved director, thereby exposing the remaining fistulous tract which is then excised, leaving a clean "gutter-shaped" wound. Wide retraction of the severed ends of the sphincter muscle is prevented by adhesion of the muscle to the block of scar tissue at the site of the primary operation. By the use of this two-stage method, sphincter function is preserved and incontinence prevented.

When the sphincter muscle itself is widely involved in the lupus type of perianal infection, operation is contraindicated, because extensive excision of sphincter muscle must result in incontinence. Fortunately, these usually

occur in toxic, advanced terminal cases whose life expectancy is short. My feeling is that a patient is happier with a perianal tuberculous lesion than with an incontinent anus.

Acute abscesses are treated early by adequate incision to drain pyogenic pus. Tuberculous granulation tissue is absent in this early stage. After two to three weeks, to allow subsidence of acute infection, the resulting fistula is excised.

Chronic, discrete circumscribed abscesses in our patients were usually tuberculous. Exploratory incision revealed little or no pyogenic pus, but typical dusky, cyanotic, friable tuberculous granulation tissue was seen comprising the walls of the cavity, with necrotic tissue filling the lumen. The entire lesion was widely excised so that no tuberculous granulations or fibrous abscess wall remained. The resultant wound should be "saucer-shaped," the base consisting of normal healthy subcutaneous fat (Fig 5). The internal opening of the communicating fistula is simultaneously excised, in the primary stage if it presents below the internal sphincter, or, if proximal to the internal sphincter, by seton and secondary operation as described.



FIG 6—Complete healing of extensive perianal abscess with multiple fistulae. Six stages were necessary over an interval of 18 months. Patient gained 50 pounds and had no recurrence in two years' follow up.

The patients that presented our most difficult therapeutic problems were those with extensive multiple lesions. These consisted of widespread, creeping or serpiginous subcutaneous abscesses, often multiple, the individual abscesses connecting with each other through one or more fistulous tracts. Most of the patients operated upon in other institutions were of this type. They came to us with draining fistulous tracts, which usually communicated with serpiginous abscesses. Multiple operations in successive stages may be necessary when the lesion is extensive. The patient shown in Figure 6 required six stages over a period of 18 months to obtain what is now a two-year cure. Planned procedures in these widespread, multiple lesions must often be altered by findings at operation. The largest area of cyanotic, edematous skin overlying a subcutaneous abscess is incised. The abscess is unroofed by excising the overlying skin, thus affording ample space for exploration. The granulation and fibrous tissue comprising the floor and lateral walls of the abscess are excised. Islands of tuberculous granulation tissue are easily distinguished in the wound by their dusky, cyanotic color. When explored with a probe these granulations usually are found to comprise the lumen of a sinus or fistula connecting with an adjacent abscess, or with an internal or

external fistulous orifice. A grooved director is threaded through the tract, which is exposed by a scalpel incision. As just stated, the tract may communicate with another abscess. The sinus tract and abscess are, therefore, excised, being careful to leave any island of uninvolved skin if possible. If the resulting wound promises to be very extensive, completion of operation is deferred for six to eight weeks to allow healing of the primary wound, in order to insure fibrous support of the perineal floor by formation of a block of scar tissue.

Occasionally, the sinus is seen to lead cephalad into the superior rectal space. In such a case, practicability counsels conservatism, inasmuch as excision of the entire tract would entail sacrificing the supporting muscles of the rectum and would result in a very extensive loss of tissue. Our procedure



FIG 7—(A) Extensive abscess widely excised showing the distal aperture of the sinus extending into the superior rectal space. Excision of the tract unfeasible, treated subsequently by chemical cauterization.



FIG 7—(B) End result.

has been to excise the abscess and sinus tract to the level of the floor of the superior rectal space. After two or three weeks, when the wound is granulating well, the remaining sinus is packed with silver nitrate stick. The eschar is removed in 48 hours. Chemical cauterization, as described, must often be repeated, the desideratum being the destruction of the tuberculous granulation tissue. End-results in these cases are satisfactory, inasmuch as the abscess is eliminated and the tuberculous sinus converted into a simple granulating sinus draining serum instead of tuberculous pus (Fig 7).

Fistulae often extend from the primary abscess, course deep in the subcutaneous tissue to emerge at a distance in a remote external fistulous opening. This tract should be widely excised, excision to include overlying skin and the external orifice. A similar procedure is used when the internal orifice of the fistula emerges in the anus distal to the internal sphincter. The external sphincter muscle is incised over a grooved director passed through the fistula at right angles to the direction of the muscle fibers. If the fistula emerges above or in the internal sphincter muscle, the two-stage excision with seton is used. Multiple combinations of abscesses, external and internal fistulae,

are commonly seen (Fig 8) Tuberculous anal ulcers are treated radically. Wide excision of the ulcer and adjacent skin is imperative to prevent extension of the lesion. Healing takes place by granulation and epithelialization.

Cautery excision of tuberculous perianal infection is advocated by some surgeons. Apparent advantages include the sealing of the afferent lymphatics, hemostasis, and complete destruction of tuberculous tissue. Despite these advantages, the cautery knife and curette were soon discontinued as a routine on our service. Their disadvantages, in our experience, consisted in the fact that isolated foci of tuberculous granulations in the wound were obscured by resultant charring. Depth of coagulation of tissue was difficult to control, postoperative slough was extensive and painful, and healing was markedly delayed.



FIG 8—Patient operated upon for fistula five years ago. (A) Present status—residual abscess in the left buttock with three external fistulous orifices and one internal orifice above the internal sphincter muscle. (B) Extensive excision of the anterior and posterior fistulous tracts and abscess. Seton shown placed through internal opening above the internal sphincter. (C) After excision of the seton—almost healed.

We do not employ methylene blue to delimit fistulous tracts, as it was found, as shown by Rogers and Hall,⁸ that besides the primary tract, all surrounding tissues became stained. This definitely obscured rather than clarified the dissection of tuberculous tissue.

Elective anal surgery, such as hemorrhoidectomy and excision of simple fissure in tuberculous patients with positive sputum, presents a problem. Of 34 such operations performed on our service, contamination of wound occurred in two patients. Biopsy from the wound margins showed tuberculous granulation tissue. Healing was delayed in four of these cases—one, 20 weeks, two, 12 weeks, and one, eight weeks. Wound contamination with tubercle bacilli in these cases was the probable explanation for delayed healing. The possibility of tuberculous skin infection, unrecognized at the time of operation, is suggested, however, by the histologic finding of tubercles in the routine biopsy of a hemorrhoid from an uncomplicated case who went on to healing in three weeks (Fig 9).

Postoperative Treatment—Postoperative reaction was surprisingly moderate considering the fact that large areas of tissue were removed, and

that hemorrhage was fairly profuse in patients with advanced tuberculosis whose general condition was poor. Temperature was slightly elevated for two or three days, pain was moderate and easily controlled by sedation.

At completion of the operation the wound is packed tightly with iodoform gauze which is removed in 48 hours. Sitz baths are then instituted twice daily, the wound being loosely packed with gauze saturated with cod liver oil. Patients are urged to be ambulatory early, this, however, depending on the extent of pulmonary involvement. Once or twice weekly, granulations are swabbed with pure phenol and when exuberant are first removed with a sharp uterine curette. Following this routine, we have had no contamination of

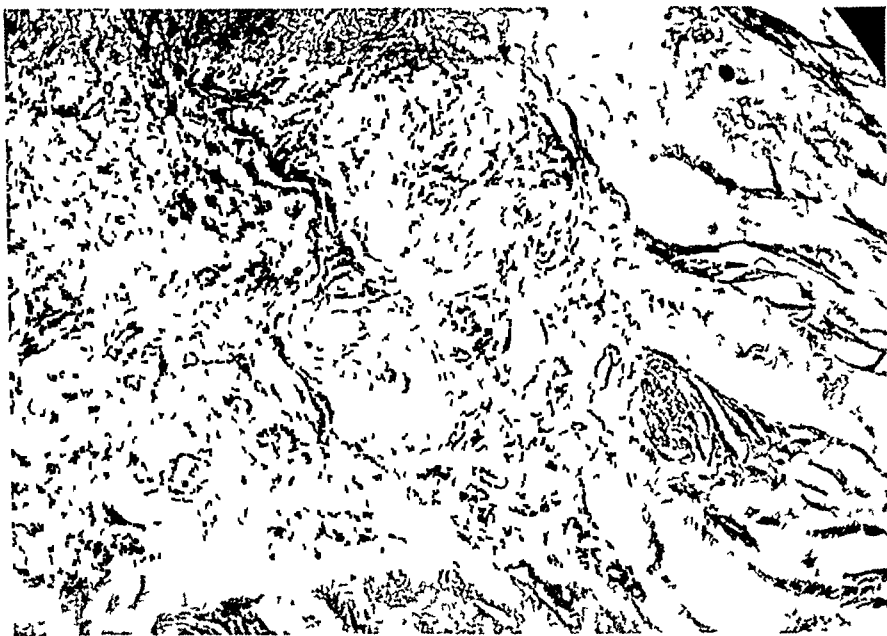


FIG. 9.—Photomicrograph showing two tubercles below the skin in a hemorrhoid of a patient with positive sputum. Preexisting unrecognized perianal tuberculosis may account for delayed healing of hemorrhoidectomy wounds in patients with active pulmonary tuberculosis.

wounds, and when primary excision has been complete, wounds have healed even in patients with marked pulmonary involvement and with high concentration of bacilli in the sputum. Pinch-grafts were necessary in one patient, in whom epithelialization appeared stationary, because of extensive resection of skin.

SUMMARY—Table IV gives the results obtained in 100 consecutive patients operated upon between April, 1935, and September, 1939. Considering only the 68 cases with proved perianal tuberculosis (positive biopsy), a number of significant points regarding this clinical entity are apparent (Table V).

In order of frequency, multiple lesions, *i.e.* abscesses plus fistulae, were most common, 61 per cent, fistulae alone, 21 per cent, acute or chronic abscess, 18 per cent. Operation was necessary in stages in 40 per cent. However, a number of patients upon whom one operation was performed on our service, had been operated upon previously in other institutions, 35 per cent.

PERIANAL TUBERCULOSIS

TABLE IV

RESULTS IN 100 TUBERCULOUS PATIENTS WITH PERIANAL INFECTIONS
TREATED BY RADICAL EXCISION OF LESION

	Positive 68	Biopsy for Tuberculosis Negative 18	No Biopsy 14	No of Cases
Pathology				
Abscess	12	2	6	20
Fistula	14	10	5	29
Abscess plus fistula	42	6	3	51
Number of operations				
1 operation	41	13	14	68
2 operations	19	4		23
3 operations	4			4
4 operations	3	1		4
6 operations	1			1
Complete healing—in months				
Less than 4 mos	33	11	9	53
Less than 8 mos	14	3	2	19
Less than 12 mos	1			1
Over 12 mos	1			1
Unhealed—in months				
Discharged				
Less than 4 mos	4	2		6
Less than 8 mos	2			2
Less than 12 mos	1			1
Died				
Less than 4 mos	3	1	2	6
Less than 8 mos	4		1	5
Less than 16 mos	1			1
Unhealed Persistent sinus	4	1		5
Weight				
Gain	39	6	4	49
Loss	10	3	2	15
Stationary	19	9	8	36
Sputum				
Positive	62	13	11	86
Negative	6	5	3	14

Cure was complete in 49 per cent in less than four months. Healing occurred in 72 per cent of 68 patients with positive biopsy for tuberculosis granulation tissue. Eight patients died and seven were discharged from the hospital with unhealed wounds. Of 53 patients with positive tuberculosis on biopsy, upon whom radical excision was performed, and who remained under our observation in the hospital, 49 (92 per cent) went on to complete healing. Of the remaining four, three patients had persistent sinuses extending into the superior rectal space, the other refused excision of a remaining superficial fistula.

which was symptomless. Weight remained stationary in 19 patients in this group, 39 gained weight, and ten lost weight after operation. Positive sputa were present in 91 per cent of this group.

TABLE V

END-RESULTS FOLLOWING RADICAL EXCISION IN 68 PATIENTS WITH
PERIANAL INFECTIONS—HISTOPATHOLOGICALLY TUBERCULOUS

	No. of Cases	Percentage
Pathology		
Abscess	12	18
Fistula	14	21
Abscess plus fistula	42	61
Number of operations		
One	41	60
Multiple	27	40
Complete healing—in months		
Less than 4 mos	33	49
Less than 8 mos	14	21
Less than 12 mos	1	1.5
Over 12 mos	1	1.5
	49	72
Unhealed—in months		
At discharge from hospital		
Less than 4 mos	4	6
Less than 8 mos	2	3
Less than 12 mos	1	1.5
	7	10
At death		
Less than 4 mos	3	5
Less than 8 mos	4	6
Less than 12 mos	1	1.5
	8	12
Unhealed Sinus persists in wound	4	6
Weight		
Gain	39	57
Loss	10	15
Stationary	19	28
Sputum		
Positive	62	91
Negative	6	9

CONCLUSIONS

(1) Perianal infections occur in 5 to 10 per cent of patients with pulmonary tuberculosis as contrasted to 0.5 per cent in the nontuberculous population. Tuberculous granulation tissue was found on histopathologic examination in 79 per cent of 86 patients in this series. Fourteen cases early in the series had no biopsy.

(2) Multiple lesions, *i.e.*, abscesses and fistulae, were the most common. Lesions were frequently extensive, and spread usually occurred along the course of the superficial perianal lymphatics.

(3) Conservative surgery is futile in the treatment of perianal tuberculosis, as shown by persistence of pathology in 35 per cent of our patients previously operated upon elsewhere

(4) Effective treatment demands radical excision of all existing pathology. Foci of tuberculous granulation tissue must be carefully sought for in the wound and completely eradicated when found. Operation in stages is frequently necessary because of the extent of the lesion. Radical procedures as described, when instituted early, should result in a high percentage of cures.

REFERENCES

- ¹ Allingham, Wm. Diseases of the Rectum 4th ed, Blakiston, Philadelphia, 1882
- ² Martin, C. L. Tuberculosis Fistula in Ano, J A M A, 101, 201, 1933
- ³ Berry, F. B. Perianal Tuberculosis ANNALS OF SURGERY, 99, 593, 1934
- ⁴ Chisholm, A. J. Relationship of Pulmonary Tuberculosis to Anorectal Fistulae Surg, Gynec and Obstet, 56, 610, 1933
- ⁵ Marino, A. W. M. Perianal Tuberculosis Read at N. Y. Proctological Society, March, 1938
- ⁶ Nesselrod, J. P. An Anatomic Restudy of the Pelvic Lymphatics ANNALS OF SURGERY, 104, 905, 1936
- ⁷ Sweany, H. C. Quoted by Martin ²
- ⁸ Rogers, H., and Hall, M. G. Pilonidal Sinus Arch Surg, 31, 942, 1935
- ⁹ Leslie, G. L. Importance of Tubercle Bacillus in Etiology of Ischiorectal Abscess and Fistula in Ano Canad Med Assoc Jour, 16, 1215-1220, 1926

INTERNAL DERANGEMENTS OF THE KNEE JOINT

AN ANALYSIS OF ONE HUNDRED CASES WITH FOLLOW-UP STUDY

L. KRAELER FERGUSON, M.D.

AND

WISLEY D. THOMPSON, M.D.

PHILADELPHIA, PA.

FROM THE HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA, PA.

IN THIS REVIEW of 100 cases of internal derangement of the knee, we wish to point out the relative frequency of the various lesions which fall under this general diagnosis, to detail the symptomatology upon which the diagnosis and operative indications are based, and to give the follow-up results obtained in 95 of the 100 cases. In addition, the operative technic and plan of after-care will be described, as well as the operative complications which have appeared.

Anatomy of the Knee Joint—The knee, although generally looked upon as a type of hinge joint, differs very materially from the true hinge joints such as the elbow and ankle. The surfaces of the condyles of the femur and the head of the tibia fit very poorly. Only in full extension is there a broad surface contact. In all other positions the articular surfaces meet only at points. The semilunar cartilages deepen the joint cavity of the tibia and accommodate it to variations in contact between the condyles and the tibia. They move backward in flexion to deepen and protect the posterior margin of the tibial head, and in extension "they follow the forward rolling of the condyles and deposit themselves in the anterior joint cavity where they become compressed and give a springy protection to the margins of the joint" (Palmer¹) (Fig. 1). Of the two cartilages, the lateral has the greater range of motion. The movement of the internal cartilage is limited by its wide fixation to the under surface of the internal lateral ligament. It is frequently caught and torn between the internal condyle and the head of the tibia, in movements in which there is internal torsion of the condyles, in the act of extending the knee. In our 64 frank cartilage injuries, 62 were of the internal and only two of the external cartilage.

The synovial membrane is thin. Its chief function is the secretion of synovial fluid which lubricates the joint and nourishes its cartilaginous surfaces. Between the synovial capsule and the infrapatellar ligament is a space filled with a fat pad which, in extension, comes to lie in between the condyles. This pad is believed by many to counterbalance the variations in pressure that occur with changes in the position of the joint. The pad responds to trauma by becoming edematous, and later forms firm fibrous "snow-capped" projections into the joint cavity.

The integrity of this relatively weak articulation is maintained largely by

Submitted for publication May 16, 1939

DERANGEMENTS OF KNEE JOINT

strong ligaments both inside and outside the joint. The crucial ligaments within the joint prevent abnormal anteroposterior luxation. Outside the joint, the strong lateral ligaments, the fibrous part of the capsule, and the tendinous insertions combine to give extreme strength to a relatively unstable bony articulation. It is probable that internal derangements of the knee joint rarely occur without some injury to the adjacent ligaments. On the other hand, repair of the internal derangement will usually relieve the repeated strains on the ligaments and permit them to regain their normal strength.

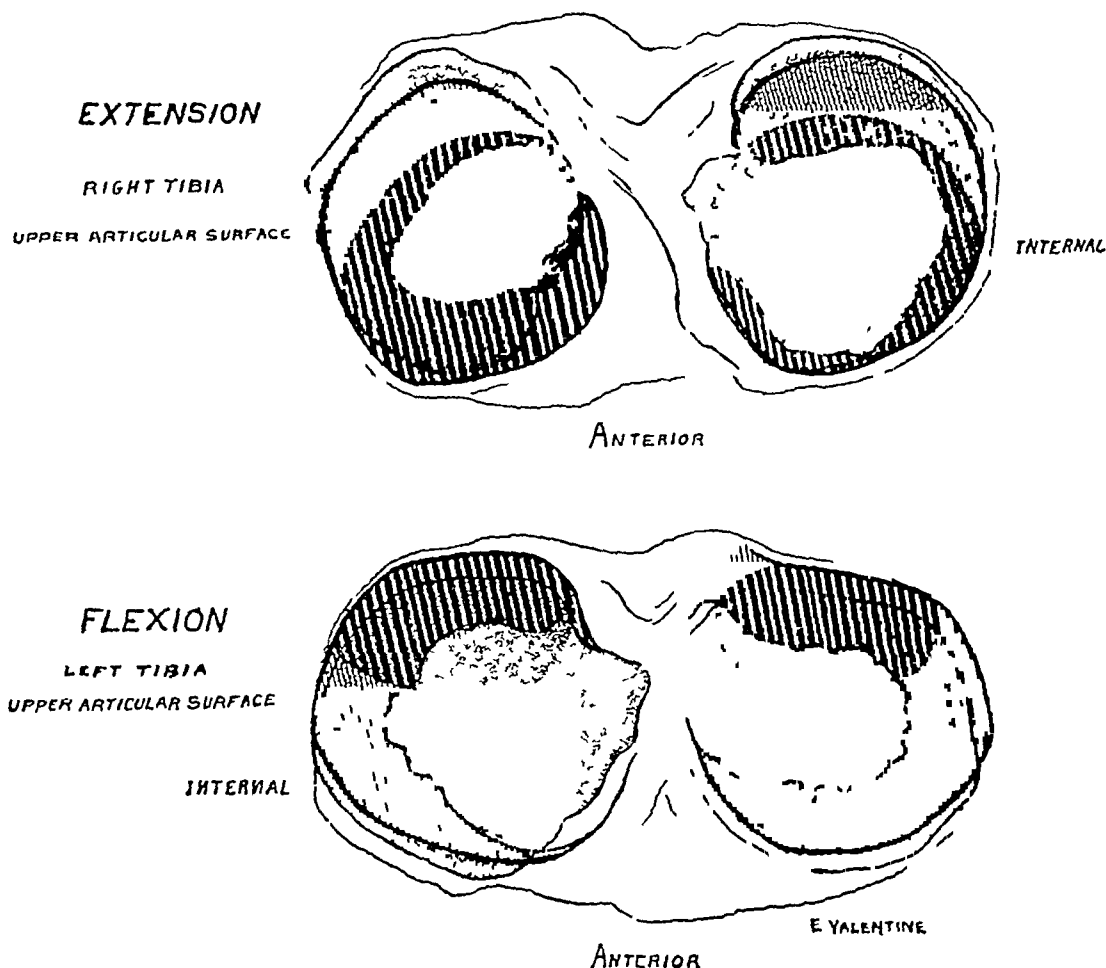


FIG. 1.—Cadaver injection specimen showing position of the semilunar cartilages, and of the articulating surfaces in the right and left knees held in extension and in flexion. The upper surface of the tibia is shown in the drawings, the shaded areas being the area of the articulating surface of the femur on the tibial head. In the upper drawing in extension the semilunar cartilages are seen to move forward and the articulating surface is along the anterior portion of the head of the tibia. In the lower drawing, in flexion, the articulating surface of the condyles is seen to be well posterior on the head of the tibia and the cartilages have moved backward away from the anterior edge of the articulating surface of the tibia.

Mechanism of Injury—The mechanism of injury in internal derangements of the knee joint is similar in almost all cases. The injury is usually indirect in which there is an internal torsion of the femur on the tibia with the knee in partial flexion. In most of our cases, the foot bearing the patient's weight was fixed on the ground and the body and femur twisted either by being struck from the side, as when being tackled or "clipped" in football, or in trying to make a sudden turn while running. This was the mechanism of injury in 65 of our 100 cases. In a smaller group of cases (15 per cent) the same mecha-

nism occurred when the foot and lower leg were twisted with the knee fixed in partial flexion, as in kicking a soccer ball

It is not surprising that 52 per cent of the injuries occurred in competitive sports, where sudden twists or body blows are not uncommon. Of these, football was the worst offender, accounting for 29 per cent. Basketball, soccer, lacrosse, jumping, baseball, tennis, boxing and wrestling each contributed its quota. Also, naturally, those injuries were more common in males—82 of our 100 cases. Of these, 68 came to operation before their thirtieth year.

FIG 2



FIG 3



FIG 2 —Adhesive strapping for the early treatment of internal injury to the knee joint. After aspiration of the effusion, a criss cross strapping is applied beginning well laterally and as high as possible on the thigh extending downward across the lower leg at the knee. Several succeeding layers are applied using two inch adhesive. The straps are anchored above and below by circular turns of elastoplast bandage.

FIG 3 —Strapping for internal injury to the knee joint. The strapping is completed by the application of a firm elastic bandage at the knee.

Early Treatment—In none of these cases, except in a few patients who came with the knee locked in partial flexion, was operation advised as a primary treatment. It has been our practice to treat the primary injury by aspiration of the knee and application of a dressing which permits fixation with function. This varied with the apparent severity of the injury. In the milder injuries, fixation was obtained by crossed adhesive strapping anchored above and below by elastic adhesive and held at the knee by an elastic bandage (Figs 2 and 3). In the more severe cases, a posterior plaster splint was used in some instances and, more recently, a castex case was applied from the ankle to the gluteal fold. It was possible for the patients to be ambulatory with these dressings, which were maintained for three to six weeks. After removal of the

strap or splint an elastic bandage was used to give partial support to the knee for an additional two to three weeks. If after a thorough trial at conservative therapy, there were frequent recurrences of knee disability, operative intervention was indicated. The average lapse of time from the original injury to operation was two and one-quarter years.

In our experience, any knee with true locking eventually came to operation. Manipulations under anesthesia, with reduction of the dislocated cartilage or the dislodgment of the foreign body, were followed by recurrence in every case.

In the study of these cases the roentgenogram did not prove of great diagnostic value except in osteochondritis dissecans or foreign body. We were unable to obtain any aid in the differential diagnosis of such difficult lesions as partial cartilage tear and hypertrophic fat pad. Our experience with arthrography has not been great, but we have depended more on clinical findings to interpret the roentgenogram rather than the reverse. Nevertheless, we believe a routine preoperative roentgenogram of the knee is indicated in every case in order that bony injury or foreign body may not be overlooked.

The injuries naturally divide themselves into four main groups according to types of pathology, *viz.*, cartilage injuries, injuries to the synovium and fat pad, crucial ligament injuries, and foreign bodies.

Cartilage Injuries—Of 100 cases of internal derangement of the knee joint, 65 showed frank injuries of the semilunar cartilages themselves. These were divided into four groups. Longitudinal tears, tears in the anterior portion of the cartilage, tears in the middle portion of the cartilage, and tears in the posterior portion of the cartilage.

LONGITUDINAL TEARS (BUCKET HANDLE)

By far the largest group, 31 per cent of the 100 cases, was comprised of patients having longitudinal tears of the cartilage, mostly of the bucket-handle type. Of these, 21 arose in competitive sports. Thirty of the patients were males. The left knee was involved in 17 cases, the right in 13 cases. The symptoms produced were fairly constant and permitted a more or less accurate diagnosis. There was marked pain in the knee joint, usually on the anterior mesial side, recorded in 27 cases. Effusion was present in almost all cases. Many patients came to the hospital at the time of the original accident with the knee locked. The others gave a definite history of locking at intervals. In a few cases, the dislocation of the torn cartilage between the condyles was reduced by manipulation, but there were recurrences every time. In those cases in which the patient came for treatment at the time of the original injury, the knee was held in partial flexion. It could not be completely extended or flexed, although there was some range of motion in the middle portion of the flexion arc. The most definite complaint was a persistent inability to extend the leg completely, due to the fixation of the torn portion of the cartilage at the anterior horn, preventing complete anterior rotation of the condyles on the

head of the tibia In one case, a patient who had his knee locked, tripped and fell, tearing loose the anterior portion of the cartilage so that at the time of operation he was able to extend the leg completely, but the cartilage was found lying between the condyles

The findings on examination in these cases varied a great deal, according to the time at which they were seen When seen early, an inability to extend the leg completely was noted and usually there was a definite effusion, although this is not invariable Those patients who were seen late, having had a history of frequent lockings, may have had no effusion whatever, but there usually was a definite area of tenderness at the inner side of the infrapatellar ligament at the head of the tibia In such cases there may or may not be some relaxation of the lateral ligaments of the joint, especially of the internal lateral ligament In the 31 cases with longitudinal tears of the cartilage the correct diagnosis was made in 30 instances The other diagnosis was incorrect in that the cartilage injured was the external instead of the internal cartilage

In all cases, the cartilage was removed as far back as possible, removing all of the detached tissue In one patient who had a history of six years' duration, there was a definite area of erosion of the cartilage over the end of the femur Twenty-nine of the 31 cases were followed (Table I)

TABLE I

SYNOPSIS OF THE 29 INSTANCES OF LONGITUDINAL TIAR FOLLOWED-UP

15-20 years of age (6 cases, 5 followed)		
Result	4 normal	
	1 has weakness, stiffness, clicking (this patient had erosion of cartilage along inner condyle at operation)	
Follow-Up Period	3 years	2 cases
	4 years	1 case
	9 years	2 cases
20-30 years of age (20 cases, 19 followed)		
Result	19 normal (2 have slight ache after extreme exercise)	
Follow-Up Period	1 year	2 cases
	2 years	1 case
	3 years	2 cases
	4 years	4 cases
	5 years	10 cases
(No relation seen between duration of symptoms and operative result in this group)		
30-40 years of age (5 cases, 5 followed)		
Result	5 normal	
Follow-Up Period	2 years	1 case
	4 years	1 case
	7 years	2 cases
	9 years	1 case

TEARS OF THE ANTERIOR PORTION OF THE INTERNAL SEMILUNAR CARTILAGE

There were 18 patients in which a tear of the anterior portion of the semilunar cartilage was found. Of these, all but one were males. The history of injury showed competitive sports to be a major factor in the causation. Fourteen tears occurred in this manner, 11 of these in football. The symptoms these patients exhibited were somewhat similar to those sustaining longitudinal tears. At the time of the injury, there was immediate pain and effusion. The knee, however, usually was not locked and, as the effusion decreased, the patient was able to get along for a time without disability. Twists of the knee, however, resulted in a recurrence of the injury characterized by a catching of the torn cartilage between the condyle and the head of the femur. As a rule, true locking did not take place, but the catching of the foreign body gave the sensation to the patient of the knee giving way underneath him, and frequently falls resulted. This symptom was so similar to that described in cases of hypertrophy of the infrapatellar synovium that it was almost impossible to distinguish between these two clinical entities. Occasionally, the torn cartilage would work itself into the space between the condyles, in which case true locking of the joint would take place.

On examination, the chief points of diagnostic importance were the tenderness along the anterior portion of the semilunar cartilage when deep pressure was made, the effusion and the definite crepitation on motion of the joint. We were unable to distinguish with certainty this type of injury from the injuries resulting in contusions of the infrapatellar fat pad, and, in diagnosing these cases, almost invariably, the diagnosis was made of an internal derangement of the knee joint, the type undetermined.

In the treatment of these tears the entire cartilage was removed in 11 cases, and, in seven cases, only the anterior torn portion of the cartilage was excised. Sixteen of the 18 cases were followed (Table II).

TABLE II

SYNOPSIS OF THE 16 INSTANCES OF TEARS OF THE
ANTERIOR PORTION OF THE INTERNAL SEMI-
LUNAR CARTILAGE FOLLOWED-UP

Under 20 years of age (5 cases, 5 followed)		
Results	5 normal	
Follow-Up Period	7 months	1 case
	4-6 years	4 cases
20-30 years of age (11 cases, 10 followed)		
Result	10 normal	
Follow-Up Period	3-10 months	3 cases
	1-2 years	2 cases
	4-6 years	3 cases
	14 years	2 cases
30-40 years of age (1 case)		
Result	normal	
Follow-Up Period	1 year	
40-50 years of age (1 case, not followed)		

In this group of cases, we were interested to note whether there was any improvement in the follow-up results in those knees in which only the anterior torn portion of the cartilage was excised over those who had the entire cartilage removed. As a matter of fact, in the entire follow-up group, all the knees were normal, indicating that a conservative operation, with simple removal of the torn portion of the cartilage, will give an excellent result (Fig. 4)

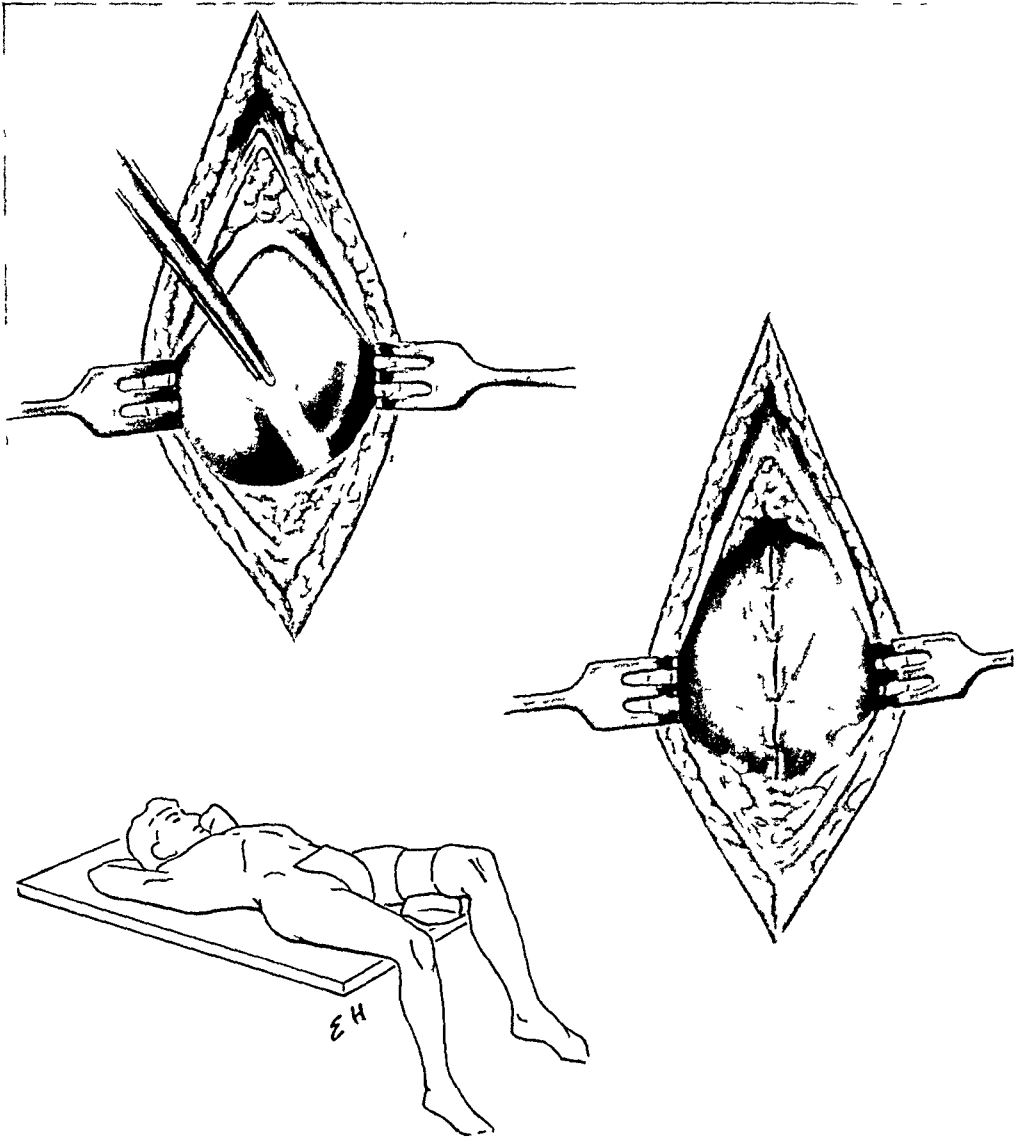


FIG. 4—Upper drawing. Case showing a dog-eared tear of the anterior portion of the cartilage. In seven patients, only this torn portion of the cartilage was removed. Good results were obtained in all instances.

Middle drawing. Showing method of loosely suturing the capsule of the joint with interrupted sutures. The loose suture permits escape of joint effusion and so prevents secondary effusions of the knee after operation.

Lower drawing. Showing position of the patient on the table, sand bag under the knee and tourniquet on the thigh. It is to be noted in these drawings that the wound covers, which are clipped to the skin edges with Michel clips, have been omitted.

TEARS OF THE MIDDLE PORTION OF THE INTERNAL SEMILUNAR CARTILAGE

There were ten cases in which only the middle portion of the semilunar

cartilage was injured either by a transverse fracture of the cartilage or by a dog-eared tear. All of these patients were male. Three of the injuries occurred in football.

There were pain, effusion and intermittent catching or locking in the knee joint in practically all cases. The patient almost invariably complained of a sensation of the knee giving way and recurrences of the disability were quite frequent. We were unable, from physical examination, to make a definite diagnosis in this group. The symptoms were almost indistinguishable from those described for anterior tears of the cartilage although it is possible that the area of tenderness on pressure over the cartilage was more lateral than noted in the anterior group. In all cases the cartilage was excised as far back as possible. All ten cases were followed (Table III).

TABLE III

SYNOPSIS OF THE TEN INSTANCES OF TEARS OF THE MIDDLE PORTION OF THE INTERNAL SEMILUNAR CARTILAGE FOLLOWED-UP

Age	Patients	Result	Follow-Up Period
20-30 years	6	5 normal 1 has occasional effusion and locking	2, 4, 10, 13, 14 years 6 years
30-40 years	2	Normal	1, 6 years
40-50 years	1	Has slight limitation of flexion	8 years
Unknown	1	Normal	5 years

POSTERIOR TEARS OF THE SEMILUNAR CARTILAGE

There were six cases in which a tear of the posterior portion of the semilunar cartilage was noted at operation. Of these five were males. The one female patient sustained her injury playing hockey. Three other cases received theirs in athletics. Again, we were unable to note any characteristic symptomatology in patients with posterior tears of the cartilage. The symptoms of pain along the inner side of the knee with effusion, locking or catching and giving way were constant in this group. The findings on examination were also similar to those described for anterior tears. There was usually pain on twisting of the leg with tenderness along the inner side of the patellar ligament. In our analysis, there were no characteristic symptoms which would permit a diagnosis of the position of a partial tear of the cartilage. Furthermore, the diagnosis was by no means easy at the time of operation. It is the suspicion of the presence of these partial tears which accounts very often for removal of the cartilage when no injury to the cartilage can be found at the anterior portion of the joint. In one of these cases the cartilage appeared to be normal and was left in place. It was necessary to reoperate upon this patient and remove the cartilage because of recurrence of symptoms. At the second operation a longitudinal posterior tear of the cartilage was demonstrated. All six cases of posterior tears were followed (Table IV).

TABLE IV

SYNOPSIS OF THE SIX INSTANCES OF POSTERIOR TEARS
OF THE SEMILUNAR CARTILAGE FOLLOWED-UP

18 years of age (1 case)

Result Feels knee is going to fall apart (has tear of
lateral ligament also, but refuses operation)

Follow-Up Period 7 years

20-30 years of age (4 cases, 4 followed)

Result 4 normal

Follow-Up Period 6 months, 1, 2, 11 years

37 years of age (1 case)

Result Normal

Follow-Up Period 2 years

LOOSE INTERNAL SEMILUNAR CARTILAGES

There was a further group of 13 cases in which, at operation, no fracture or dislocation of the semilunar cartilage was found, but there was a very definite looseness of the cartilage (looser than the operator considered normal), and in some of these cases a definite tear of the coronary ligament was demonstrated. These patients frequently had, in addition, definite hypertrophy of the infrapatellar fat pad and adjacent synovium. The question as to whether the looseness of the cartilage produced the disability in the knee joint or whether the hypertrophied fat pad was the cause of the symptoms is still undecided. In this group, there were seven males and six females. Six of the injuries occurred in football, one in boxing, one in tennis and one in tap dancing. The history of these patients was similar to that given for the partial tears of the cartilage. In 11 patients, there was a definite history of pain with effusion in the knee joint. The effusion gradually subsided, but there remained a limitation of extension in some cases, a crepitation in a few. In eight patients there was a history of the leg giving way, and in eight there was a definite history of recurrence of symptoms following a twist of the knee. On examination, the patients presented pain on the inner side of the patellar tendon with tenderness on pressure over that area. There was usually some slight fullness of the knee if the patient was seen soon after an injury or a recurrence. There were no other characteristic diagnostic symptoms. As a result, the diagnosis of internal derangement of the knee joint was usually made because a definite pathologic diagnosis was almost impossible from an examination of the patient or a history of the course of his disease.

Eight patients were treated by excision of the cartilage and the hypertrophied fat pad. In four cases, the cartilage alone was excised and, in one case, an attempt was made to suture the coronary ligament at the site of its injury. All of these patients have been followed (Table V).

In reviewing the follow-up results in this group of cases, we have reached the conclusion that in those patients in whom the internal semilunar cartilage appears loose, but in whom there is also a definite hypertrophy of the synovial

DERANGEMENTS OF KNEE JOINT

TABLE V

SYNOPSIS OF THE 13 INSTANCES OF LOOSE INTERNAL SEMILUNAR CARTILAGES FOLLOWED-UP

Under 20 years of age (2 cases)

Result 1 has slight swelling (coronary ligament sutured at operation)

1 has weakness, swelling, giving way, crepitation (fat pad not removed)

Follow-Up Period 1 and 2 years

20-30 years of age (8 cases)

Result 8 normal

Follow-Up Period 3-6 months 2 cases
1 and 2 years 1 each
5-7 years 4 cases

Over 30 years of age (3 cases)

Result 2 normal

1 not quite normal (fat pad not removed)

Follow-Up Period 1 year 1 case
2 years 2 cases

infrapatellar pad, an excision of the fat pad should be performed as well as removal of the cartilage. As a matter of fact, it is our belief that in all probability the causation of the symptoms in these patients is more often due to the hypertrophied fat pad than it is to the looseness of the internal semilunar cartilage.

HYPERTROPHY OF THE INFRAPATELLAR FAT PAD (SYNOVITIS)

The second group of cases of internal derangements of the knee joints showed a definite hypertrophy of the infrapatellar fat pad without any injury



FIG 5—Patient showing the limitation of extension in hypertrophy of the infrapatellar fat pad

to the cartilages of the joint. In this group were 16 cases, nine of whom were males and seven females. Nine gave a history of having had a twist when falling. Four of the injuries occurred in sports. Pain and effusion were present in all cases. In addition, there was a history of limitation of extension

in most cases (Fig 5) The sensation of giving way was a frequent symptom, and recurrences were quite the rule Many of these patients gave the history of pain, especially on going up and downstairs, more frequently on going downstairs when they put the affected leg down and began to bear their weight on that leg Most of them complained of pain on slight twists of the knee On examination in the acute stage, there was definite effusion with tenderness on either side of the patellar ligament There was perhaps a more marked fulness on each side of the ligament in these patients, although this finding was a relative one and somewhat difficult to demonstrate clinically In the quiescent stage, the area of tenderness was closer to the patellar tendon than was present in the cases of anterior tears of the semilunar cartilage, although this finding also was difficult to be sure of in a clinical examination In those cases in which there was a definite hypertrophy of the infrapatellar pad, there was oftentimes a slight limitation in extension as compared to the normal, but in some cases this finding was quite indefinite These patients were operated upon with the diagnosis of chronic synovitis in six of the 16 cases, in five cases, an indefinite diagnosis of internal derangement of the knee joint was made and, in four cases, a definite diagnosis of fracture or dislocation of the internal semilunar cartilage was made It is obvious that the diagnosis of this lesion was a great deal more difficult than the diagnosis of a fracture of the semilunar cartilage There did not seem to be any definite clinical finding present on examination which would make a certain diagnosis possible

At operation in 12 of these cases, the fat pad was excised In two, a complete and thorough examination of the joint was made and the joint closed without any intra-articular surgery In one case, the internal semilunar cartilage was removed in the fear that there might be a posterior tear of the cartilage In another, which was an operation for recurrence, a foreign body was removed in addition to some of the hypertrophied synovium Of these 16 cases, all but one were followed (Table VI)

TABLE VI

SYNOPSIS OF THE 15 INSTANCES OF HYPERTROPHY OF THE INFRAPATELLAR FAT PAD (SYNOVITIS) FOLLOWED-UP

Under 20 years of age (4 cases, 4 followed)

Result 3 normal

1 has slight weakness

Follow-Up Period 6 months-1 year 2 cases

3 years 1 case

5 years 1 case

20-30 years of age (8 cases, 7 followed)

Result 4 normal

3 fair

Follow-Up Period 2-8 months 3 cases

2 years 2 cases

3 years 1 case

7 years 1 case

DERANGEMENTS OF KNEE JOINT

TABLE VI—(*Continued*)

30-40 years of age (3 cases, 3 followed)		
Result	3 normal	
Follow-Up Period	6 months	1 case
	2 years	1 case
	9 years	1 case
51 years of age (1 case)		
Result	slight pain on extension	
Follow-Up Period	6 months	

In the three cases in the 20-30 age group considered to have fair results, there is a recurrence of swelling upon twisting the knee and an occasional sensation of giving way. One patient, who had had two previous operations in which both cartilages had been removed, had developed a hypertrophic synovitis with the appearance of a foreign body. The foreign body was removed and the hypertrophic synovium excised, and this patient still has a slight ache in the joint operated upon, with some crepitation. However, he works as a lifeguard and has a fairly normal knee. In this case, we had an opportunity to observe the area of the semilunar cartilages some years after their removal. There was an apparent regeneration of the cartilage, or of fibrous tissue in place of the cartilage, which served to take its place fairly well.

These cases with hypertrophy of the infrapatellar fat pad and those with loose internal semilunar cartilages are hard to diagnose and it is difficult to determine what treatment should be given. In the former group, we excised the cartilage in 12 of the patients, and in those cases a relatively good follow-up result was obtained. However, in two cases, we closed the knee without any operative intervention whatever, and both of these cases have shown excellent follow-up results. This leads us to speculate as to whether the operation of removal of the hypertrophic fat pad is the essential factor in producing a good knee, or the operation, by producing scar tissue and tightening up upon the fibrous capsule of the joint, has produced the good result. Too, the period of three to four weeks of relative immobilization may be sufficient to produce a subsidence of the edema and swelling of the fat pad which would remove the obstructing tissue and thereby relieve the disability.

INJURIES TO THE CRUCIAL LIGAMENTS

There were four patients who had injuries to the crucial ligaments. All of these were males. Three of the injuries occurred in football, and one patient gave the history of an injury the result of wrenching the leg. Pain and effusion in the knee joint were present in all cases. There was some limitation of motion in two. There was a sensation of giving way in the knee in two cases, and in all there were recurrent attacks of disability in the joints following twists. In none of these cases was there any particular laxity on anterior or posterior motion of the leg on the femur, and in no case was there a diagnosis of a tear of the crucial ligament made before operation. As a matter of fact, all were operated upon with the diagnosis of internal derangement of the knee joint. At operation, injury of only the anterior crucial ligament was found. In one case the ligament was partially torn and in the others it was

completely torn across. In two patients there was also a tear of the internal semilunar cartilage and in one there was a definite hypertrophy of the infrapatellar fat pad. It is questionable whether the tear of the ligament was accountable for the patient's symptoms in any of these cases.

At operation, the torn cartilage was excised and the torn ligament trimmed in two cases. In the third case, the hypertrophied fat pad was excised and the ligament was trimmed, and in the fourth there was an attempt made to repair the torn ligament. Three of these patients were followed, one for five and two for two years. All of these patients presented normal knees. They stated they are able to enter into sports without difficulty although two occasionally wear elastic knee-caps when engaging in strenuous sports.

OSTEOCHONDRITIS DISSECANS AND FOREIGN BODIES IN THE KNEE JOINT

There were five cases in which the diagnosis of osteochondritis dissecans was made or in which there were foreign bodies in the knee. All were males and, except in one case, there was definite history of injury. In one instance there was a history of direct trauma. In three others the injury occurred in football or basketball.

The symptoms were similar to those that have been characteristic of the other lesions of the knee joint—pain, effusion and crepitation. Locking was present in two cases, and there were numerous recurrences of disability in all. In these cases, more than any other, the roentgenogram is helpful in making the diagnosis. In two of them the roentgenogram was negative, in two, a definite area of rarefaction along the inner condyle was found, and in one case definite foreign bodies were demonstrated in the knee joint. The diagnosis was made on the basis of the roentgenogram in three cases. In the other two cases, in which the roentgenograms were negative, the diagnosis was internal derangement of the knee joint.

The physical signs differed in no respects from those present following injury to the cartilages or hypertrophied fat pads. When locking occurred, as it did in one patient, it was more frequently complete with absolute immobility of the knee joint, than is the case in tears of the internal semilunar cartilage of the bucket-handle type. Otherwise, the symptoms of pain and tenderness on pressure along the internal aspect of the infrapatellar ligament were the outstanding clinical findings.

At operation, in one case, multiple small fragments of cartilage were removed as well as the internal semilunar cartilage. In two cases, definite joint mice were removed and the hypertrophied infrapatellar fat pad was also excised. In one of these, a definite loose area of cartilage was removed from the mesial side of the internal condyle. In another case, although there had been a diagnosis of osteochondritis dissecans made roentgenologically, no area of loose cartilage and bone was found in the condyle.

The operator simply clipped some synechia extending between the joint capsule and the edge of the condyle of the femur. In one case, there was a recurrence of the foreign body. This was definitely a case of joint mice due to synovial osteochondromatosis. The results in these five cases are relatively

good In four cases the joint is normal three, four, five and 12 years after operation In one case there is a fair result, although the patient says he still has a catch but no swelling in his joint He shows a very good knee on examination He is a contestant in a compensation claim which may be a factor in his disability

COMMENT—Of the 100 patients operated upon for internal derangement of the knee joint, 96 have been followed-up and, of this number, only one is not satisfied with the result This patient says he feels as if his knee were going to fall apart, which adequately describes his condition, as he has a definite relaxation of his lateral ligament which should be repaired With the poor result following his previous operation, however, he is unwilling to undergo further operative intervention

Frequently, it is asked whether operation upon the knee joint does not result in a stiff knee or in the development of a chronic arthritis It is impossible to answer this question absolutely, but the follow-up results in this series of cases would permit one to feel that the answer should be in the negative Many of the patients in whom a poor result was predicted have obtained an excellent functional and anatomic knee In some cases, there has been a period of six months to a year in which some amount of disability in the knee has persisted, but this disability has gradually disappeared and a normal knee function obtained The age of the patient at the time of operation or the duration of the symptoms did not seem to materially influence the end-result unless there were associated changes in the articular cartilages of the femur

As to the question of arthritic changes in the knee joint, there is only one case in which any evidence of this type of change has appeared This patient had been operated upon twice previous to his coming to the University Hospital, and the internal and external semilunar cartilages had been removed Because of persistence of his symptoms, he was operated upon again, at which time, there was a definite panus above the condyles of the femur and evidence of an hypertrophic arthritis along the edges of the condyle He later developed a foreign body in the knee joint This was removed, and since that time his knee function has been good, although he still has slight discomfort It should be pointed out that in these operations on the knee, definite changes in the cartilage over the condyle of the femur had been seen in three cases, and there was an osteochondritis dissecans apparent at the time of operation in three others It would appear, therefore, that the operation does not necessarily produce arthritic changes but that the injury to the joint and cartilage and the persistence of disability in the knee joint may be factors in the production of an arthritis if the arthritis does appear (Fig 6)

The Operative Procedure—In preparation for operation no special pre-operative technic is used other than that ordinarily employed for any celiotomy Spinal anesthesia was employed in the large majority of these cases and was found extremely satisfactory for this type of operation As a rule, no more than 100 mg of procaine is necessary, and frequently a unilateral

anesthesia may be obtained. A rubber band tourniquet is applied, beginning at the toes and extending upward to the thigh where it is fixed as a circular tourniquet with several layers. The band is then removed from the foot and leg and a cadaveric anemia is produced. The skin is prepared by one application of an antiseptic solution. The patient's knee is bent over a break in the table. The lower leg is wrapped in a sterile sheet bandaged in place so that it can be manipulated throughout the operation at the will of the operator. An incision about two inches long is made, beginning at about the middle of the patella to the mesial side and extending downward

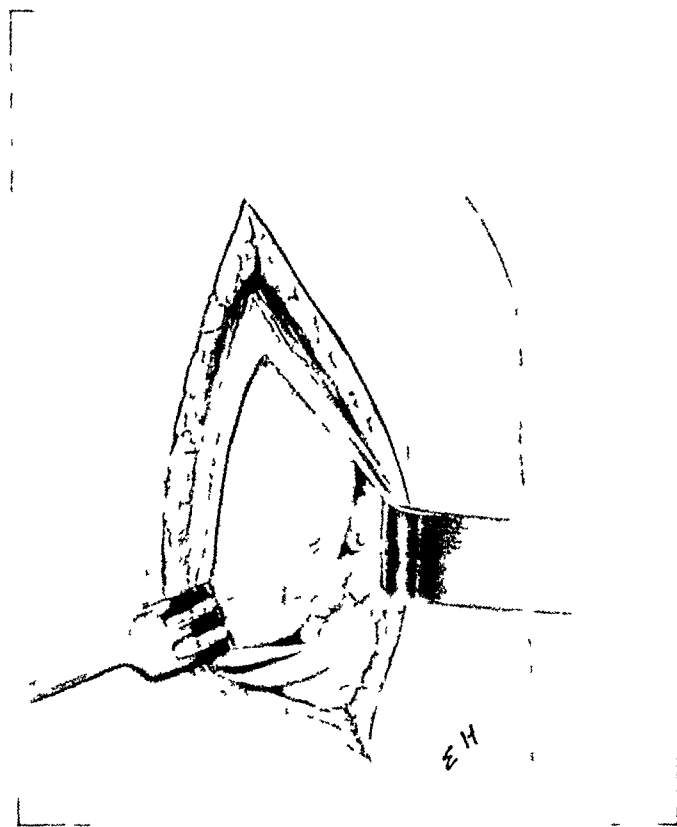


FIG. 6—Drawing showing marked hypertrophy of the infrapatellar fat pad with erosion of the adjacent cartilage on the condyle of the femur. Duration of symptoms in this case—one year. Erosion of the cartilage on the head of the tibia was also noted in this case.

over the head of the tibia. After incision of the skin and superficial fascia, towels are applied with Michel clips, and the wound is thus protected from skin contamination. After changing knives, the incision is continued through the capsule, thus opening the joint. As a rule, the Lane technic is employed. An aspirator is used for removal of the joint fluid and whatever blood may appear, although bleeding is almost absent throughout the entire operation. Through this opening, the exposure is sufficient to permit inspection of the mesial side of the joint and, if necessary, the incision may be continued upward to dislocate the patella. We have found the curved No. 12 Bard-Parker knife to be extremely useful in excision of the semilunar cartilage. With this knife the excision may be carried around the condyle of the femur

and then by constant tension upon the loose cartilage, it may be brought underneath the condyle and so almost completely removed. In our experience, it has been found unimportant to remove the extreme posterior corner of the internal semilunar cartilage since this area never gives subsequent trouble in the joint. The hypertrophic fat pad is removed by grasping it with a hemostat or forceps and excising it with the curved knife. Rarely is there sufficient bleeding after this procedure to necessitate ligature, although occasionally a fine catgut suture has been employed to unite the severed synovial membranes.

In closure of the joint, we have followed Bohler's² suggestion not to make a complete and snug suture of the synovial capsule. This is done purposely with the idea that postoperative effusion in the joint can thus be prevented. The infrequency of effusion following these operations has proven the value of this procedure. The fascia in front of the joint is then firmly united with interrupted catgut sutures. At times, it is possible to overlap this structure and so produce a tightening of the fibrous capsule along the inner side of the joint. It is possible that this procedure may account for some of the beneficial results obtained in these operations. Wound closure is accomplished with clips.

For a time, all of these operations were followed by the application of a posterior plaster splint. Recently, the splint has been dispensed with and a simple pressure bandage applied, usually one layer of cotton batting extending for about six inches above and below the knee overlaid with a firm gauze bandage fixed in place with adhesive. The results, as far as effusion or end-result are concerned, have been equally as good with this method of treatment as with the more cumbersome splint application. The patients are kept in bed for two to five days. The average in the 100 cases has been 4.7 days. As a rule, the skin clips are removed on the fifth day and the patient allowed out of bed with crutches. The pressure dressing is continued by the application of an elastic bandage and the patient is encouraged to assume gradually normal weight-bearing on the leg. The crutches are usually continued for about two weeks after discharge from the hospital, after which time they may be dispensed with. The elastic bandage, however, is continued for at least three weeks after leaving the hospital. Many of these patients are back at their normal activities, with normal knee function, within three to four weeks following operation.

In the 100 cases operated upon there were ten wound complications. Seven of these were small serum collections or hematomata, and three were small stitch abscesses. Effusion in the knee joint necessitating aspiration occurred in two cases. There were other minor effusions which were not treated. There were two cases with respiratory complications, and no deaths.

SUMMARY AND CONCLUSION

(1) Internal derangement of the knee joint is usually caused by an internal torsion of the femur on the tibia with the knee in partial flexion.

(2) Eighty-two per cent of our patients were males, and in more than

half of our cases the injury occurred as an accident of competitive sports

(3) Longitudinal tears of the internal cartilage were the most frequent injury (31 per cent). Removal of the cartilage resulted in a normal knee in 28 of 29 cases followed-up

(4) Tears of the anterior portion of the cartilage were found in 18 patients. There were 16 patients followed, all have normal knee function. The results are equally good with partial or complete excision of the cartilage

(5) Tears of the midportion of the cartilage occurred in ten patients. Eight patients followed have normal knee function after excision of the cartilage. One has slight limitation of flexion, and one has occasional catching and effusion

(6) Posterior tears of the cartilage occurred in six patients. Five patients have good function of the knee after removal of the torn cartilage. One patient has a poor result because of definite relaxation of the ligaments of the knee

(7) Abnormal looseness of the internal semilunar cartilage was found in 13 patients. In most of these cases there was also a hypertrophy of the infrapatellar fat pad. Excision of the internal cartilage, with or without excision of the hypertrophied fat pad, was performed. In ten patients the knee function is normal. In three cases, in which the fat pad was not excised, there is slight residual disability

(8) Hypertrophy of the infrapatellar fat pad was found in 16 cases. In 15 cases followed, ten patients have normally functioning knees and five have occasional disability on twisting the knee. In two of the good results the fat pad was not excised

(9) Injuries to the anterior crucial ligament occurred in four cases. In only one of these was an attempt made to repair the ligament. Good results were obtained in all cases

(10) Osteochondritis dissecans or foreign bodies were found in five cases. Four of these have good results, one patient has slight residual disability

(11) A plan for operation and after-care is described in which the essential points are: No special preparation of the knee, spinal anesthesia, bloodless field, loose suture of the synovial capsule, pressure bandage without splint, early ambulatory after-care with early weight-bearing

Conservatism, aspiration and fixation with function should be employed as a primary treatment. Recurrences of knee disability, especially locking, effusion and giving way, are indications for arthrotomy

The authors wish to acknowledge with thanks, the privilege of reporting some cases from the services of Doctors Eliason, Muller and Ravdin at the University of Pennsylvania Hospital, Philadelphia, Pa

REFERENCES

- ¹ Palmer, Ivar. On the Injuries to the Ligaments of the Knee Joint. *Acta Chir Scandinav*, 81, 1-282, 1938
- ² Bohler, L. Meniskusverletzung. *Wien Klin Wchnschr*, 37, 972-977, 1938

SOME PHYSICAL FACTORS REGARDING CATGUT LIGATURES AND CATGUT KNOTS

A PRELIMINARY REPORT

CYRUS F HORINE, M D

BALTIMORE, MD

THE CONCENTRATION of thought since the work of Lord Lister on the sterilization of catgut appears to have been directed toward the sterility, physical chemistry and tensile strength of the material. Some simple and elementary factors regarding the proper application and the nature of absorption or hydrolysis, *in vivo*, seem to have been almost entirely overlooked. In 1922, the author reported a method of intestinal anastomosis, the principal feature of which is the occlusion of the diaphragms of severed intestine during the completion of the anastomosis by using purse-string sutures with releasable knots. Elementary information, derived concerning the reliability of the release knots in that operation, stimulated further studies on catgut knots and sutures. A very complete review of the literature upon the subject has been presented by Bulloch, Lampitt and Bushill² (1929) and Rhodes, Hottenstein and Hudson¹⁶ (1937). Taylor¹⁷ (1938) is the first to report on thorough experimental work on catgut knots.

Absorption or Hydrolysis of Catgut—The varied and divergent results of different experimenters make it important to review some of the reports. Callender³ (1874) found a diminution in the size of catgut 24 hours after implantation in the tissues. Reduction to threads was noted in 45 hours, while loops had given way in 60 hours. Macewen¹⁴ (1881) observed that chromic catgut became softened in 14 days, on an average, with a minimum of nine days and a maximum of 19. Claudius⁴ (1906) implanted some of this material in various tissues of rabbits. In the eye, absorption took place without evidence of cellular activity or leukocytic emigration. He believed that the same thing occurred in the peritoneal cavity. Iodine sterilized catgut was absorbed more quickly than carbolyzed but more slowly than that which had been sterilized by dry heat. He stated that iodine catgut disappeared in the anterior chamber of the eye within six days. He also concluded that leukocytic reaction, when it occurs, is mainly due to the chemical difference between the catgut and the surrounding tissue. Ilyin¹¹ (1908) stated that catgut lost its continuity in five days when buried in the superficial layers of the skin. In deeper layers of tissue iodine catgut ligatures were dissolved in seven days and heat sterilized material in six days. In the linea alba the continuity was lost in 14 days and no traces were found after 30 days. In muscle tissue, heat sterilized material was destroyed in seven days while iodine treated catgut lost its continuity, only, in 14 days. In entero-enterostomy both heat and iodine treated catgut lost

its continuity in six days. Number 3 catgut of both types inserted into the submucosa was absorbed in two to three days. The actual changes preceding the disappearance were slight swelling and loose texture. Goris and Rolland⁵ (1917) concluded that the treatment of catgut with chemicals does not necessarily increase the durability of the material. Macrophagic penetration takes place along the fissures of torsion. The rapidity of absorption depends primarily on the physical rather than the chemical treatment of the material. In the less adherent material absorption occurs more rapidly.

Bulloch *et al*² state "The manner of experimentation, the preparation of the catgut, the tissues into which the catgut has been implanted and the animal have been varied. The study of the literature on catgut gives no support for the statements that catgut persists for 20, 30 or 40 days in the body, as so many manufacturers of catgut assert."

Very little information is to be found on the absorption of catgut in terms of its tensile strength, except in the writings of Booth¹ (1894), Phillips¹⁵ (1914), Howes¹⁰ (1928), Kraissl and Meleney¹³ (1934), Rhodes, Hottenstein and Hudson¹⁶ (1937) and Jenkins¹² (1937).

Some Physical Factors on the Preparation, Application and Absorption—The divergent reports and controversies about catgut as a suture material are, no doubt, in many instances due either to the particular method of preparation or, perhaps more so, to the faulty application of the material.

Bulloch and his coworkers² (1929) have made many extensive studies on various physical constants, such as the number of twists per inch of the catgut ligature and their relation to the tensile strength of the material. Other physical factors in their work are quoted in certain experiments with iodized catgut where it has been wound on glass tubes. "This was done because of the possibility of the aqueous solution causing the ligature to untwist." Their results show very conclusively that ligatures wound on glass tubes are distinctly stronger than those which have not been wound. The ligatures which were simply looped were found to swell and even after remaining in the alcohol-glycerol solution for some time they were still about one size larger than the original grade. An examination of the ligatures which had been wound on the tubes showed that they had not swollen appreciably but they had become rather square in cross section, suggesting that they had shrunk and become compressed on the tube. These results confirm previous conclusions that it is important that the ligatures should be under tension during sterilization. It was evident in this last experiment that the ligatures not under tension had swollen considerably and consequently the length decreased.

Among other things, the reliability of the material depends upon the rate of absorption and largely upon the reliability of the knot. The tying of a knot is, after all, a matter of increasing the twist. It is a very exacting procedure of simple detail. Maximum efficiency can be gained only by the use of the so-called reef or square knot. There is but one general method to tie this knot so that the twist in the catgut suture material shall be re-

tained, if one takes into consideration that the material, as a general procedure, is spun in the clockwise direction. The method is demonstrated in Figure 2.

We believe the most important factor in the absorption of the material is the loss of retention of the twist in the catgut. Certain experimental and clinical data are presented herewith to demonstrate the influence of the twist upon the absorption of the material and the reliability of the knot in the catgut ligatures.

FIG 1

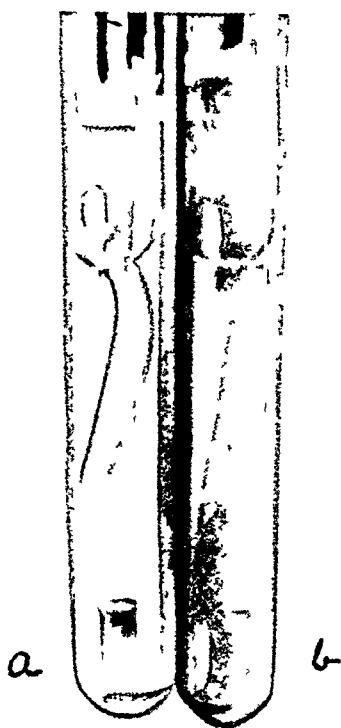


FIG 2

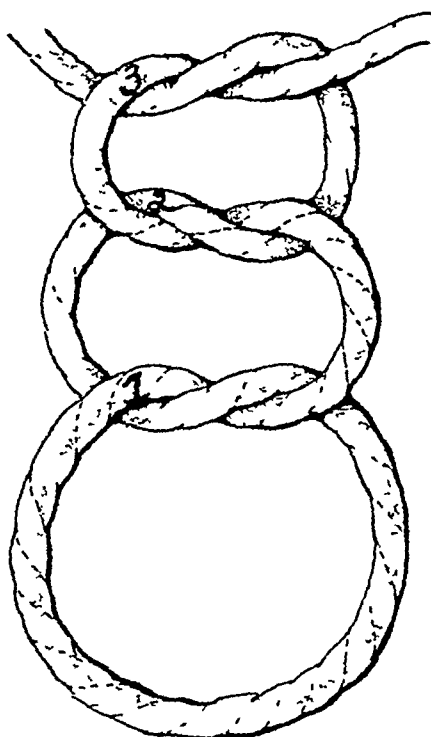


FIG 1—Photograph of a tube of No. 1 plain (a) and a tube of No. 1 chromic (b) nonboilable catgut of a popular brand. Note the counter clockwise twist in this conventional method of winding. The resultant loss of twist exposes more surfaces of the material to the effect of the tissue juices, consequently a more rapid hydrolysis.

FIG 2—Triple throw square or reef knot. The first throw (1) is in the "right hand" or clockwise direction, corresponding to the direction of the twist in the conventionally twisted catgut. This throw should be tied with sufficient tension so as to barely approximate the tissue margins. The second throw (2) is applied in the "left hand" or counter clockwise direction. It is tied with pressure sufficient to lock the first throw. The third and final throw (3) is tied in the clockwise direction as in the first loop. It may be tied with considerable tension.

This is the ideal catgut knot. It should be used consistently in clockwise spun material. The first or original throw of a catgut knot should never be applied counter clockwise to the twist in the ligature material.

Experimental Observations—The exposure of catgut to boiling temperatures, in the presence of moisture, converts the collagen into gelatin, with a consequent loss of tensile strength. The surgeon receives the nonboilable material after it has been dehydrated, sterilized and packed in a storage solution containing a small amount of moisture. It absorbs additional moisture from the tissues when introduced into the wound. This absorption causes a swelling of the catgut in its transverse diameter and produces, to a varying degree, a loss of twist in the material. The loss of twist or separation of strands exposes more surfaces of the ligature material to the in-

fluence of tissue juices. A more rapid dissolution of the material may then be expected.

Of the many methods of winding and packing the material, the most effective is the winding of the catgut on a cone-shaped instrument or tapered bobbin. In our experiments, the material was wound transversely to the instrument in smoothly curved, compact spirals beginning at the base of the bobbin and continuing from this point to the apex of the cone. Care has been taken also to twist the catgut clockwise upon its long axis as it is

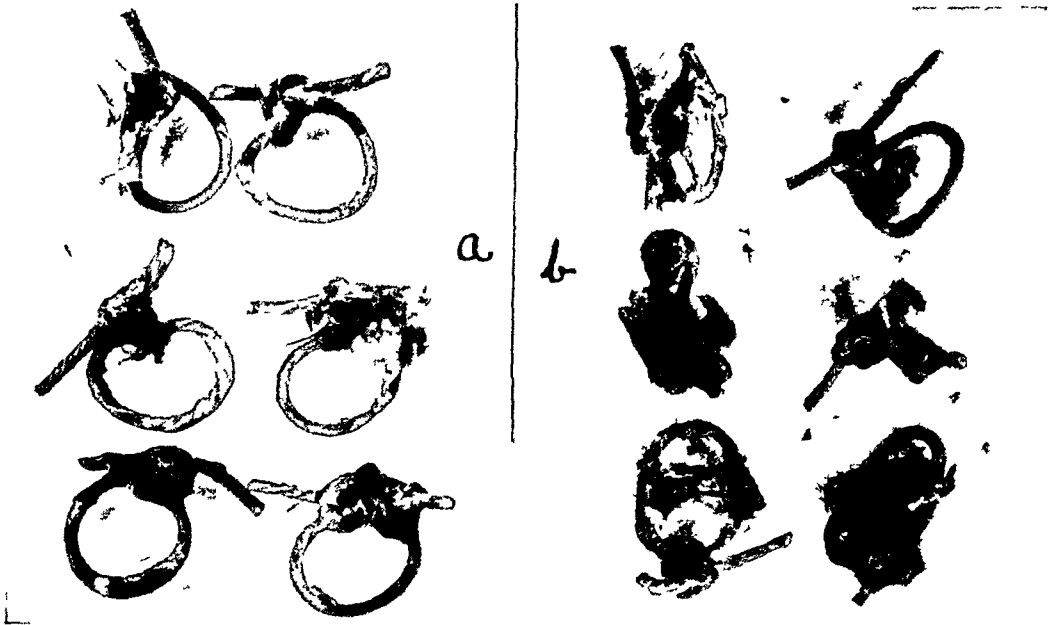


FIG 3.—Photographs of knotted loops of catgut after they had been imbedded in the abdominal wall of a guinea pig for 96 hours. All of the knots were tied under five pounds' tension before introduction into the wounds. All of the loops were taken from the same 60 inch strand of material (a) From the conventionally wound material, and (b) from the spirally wound catgut on a cone shaped bobbin.

Note the increased diameter of the material. (a) Swelling is probably due to more rapid absorption of moisture and separation of fibers. In (b), note the marked twisting on the long axes.

wound around the cone. This gives the cone-shaped or spiral strand of suture material, the diameter of the spiral decreasing from the base toward the apex. When the catgut is withdrawn and tension made on the material to draw it to a relative straight condition, thus flattening the coils, there is an increase in the amount of twist originally applied to the strand in its manufacture.

Number 1 chromic catgut, of several manufacturers, has been used in these experiments. The material was removed from the tubes, wound in the manner described above and placed in 95 per cent alcohol until used. It was prepared under strict aseptic conditions and buried in the wounds of animals.

In one series of experiments, material was taken from the tube of a 60-inch strand and divided into two equal parts. One-half of the material

was then wound with the increase twist procedure. Knotted loops were made from both pieces of the material and tied under five pounds' tension. These loops were inserted into the abdominal wall of guinea-pigs and specimens taken at various intervals (Fig 3). Experimental loops of the twisted material were found to be turned upon their long axes while the standard material remained almost circular after several days' stay in the wound. The loops of twisted gut withstood digestion and retained their continuity, on an average, five days longer than the loops made from the conventional material.

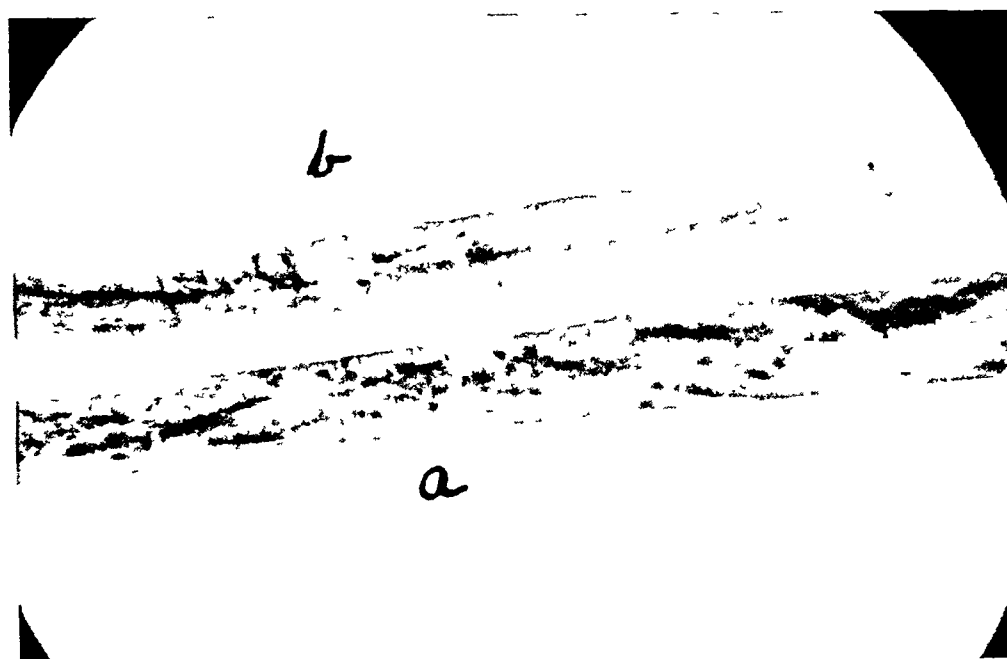


FIG 4—Photomicrograph following the 2 per cent trypsin tension test. (Mounted in gum damar.)

Both segments were taken from the same 60 inch strand of material. (a) From material which had been spirally wound on a cone shaped bobbin, (b) from the conventionally wound material.

These strands were threaded through capillary glass tubes, equal tension exerted on both, by means of mercury weights and then exposed to 2 per cent trypsin solution for a period of 48 hours.

Note the smaller frayed strand (b), in comparison to the experimental or spirally wound material (a).

In a series of experiments, straight strands of short, free pieces of conventionally wound material were buried in the abdominal wall of the dog along with an equal number of knotted loops of the same material. They were examined ten days later. In nearly every instance the loops were found, but practically all of the straight pieces of material had been absorbed. It is reasonable to assume that the knots preserved the twist in these loops. The loss of a knot in a ligature, with subsequent rapid absorption, may explain the absence of catgut so frequently encountered in cases which come to autopsy a few days after operation.

Trypsin Tests—Sixty-inch strands of No. 1 chromic catgut were equally divided and one portion wound in accordance with the method described above. Small capillary glass tubes of equal length and diameter were

threaded over segments of both wound and unwound strands, which were then exposed to equal amounts of tension by means of mercury weights. These strands were then placed under the dissecting microscope, side by side, and 2 per cent trypsin solution introduced into the glass tubes by capillary attraction. Within a few minutes, considerable debris could be seen in the solution containing the conventional catgut material, while little precipitate was to be observed in the tube of the twisted strand. The diameter of the



FIG 5—Photomicrograph of nonboilable No. 1 chromic catgut which had been placed in the peritoneal wound of a dog for a period of ten days. (Mounted in gum damar.)

One half of the wound had been sutured with a continuous suture which had been taken from the conventionally wound material. The other half was sutured likewise with catgut which had been spirally wound on a cone shaped bobbin. Both strands were obtained from the same 60 inch strand of material.

The knot (a) and its continuous portion is the spirally wound or experimental suture material, while the knot (b) and its continuous strand was taken from the conventionally wound catgut.

Note the difference in diameters and structure of the two sutures after ten days' stay in the wound.

conventional or control material was considerably less than that of the twisted material after two days' exposure to the solution. The surfaces of the standard or control strands were frayed and had a moth-eaten appearance. The digestion of the other material was slower and more uniform, the strands presented a smoother appearance (Fig 4).

Number 1 chromic catgut was used in the peritoneum of rectus incisions of 196 dogs operated upon from 1927 to 1933, inclusive. Thirteen dogs with

infected wounds were discarded. The peritoneal wounds were sutured with catgut taken from the same strand in each individual experiment. One-half of the wound was sewed with a continuous suture of the conventionally wound material and the remaining half closed with the special twisted catgut. The wounds were reopened in ten days to two weeks after operation. Practically every animal showed remnants of varying degree of thickness of remaining catgut of both materials after ten days' stay in the wound.

In 16 experiments, there had been a separation of wound surfaces with adhesions of abdominal viscera in the portions sutured with the conventionally wound catgut. In the areas sutured with the special twisted material, four such instances were to be found. Adhesions of lesser degree were found in ten other cases of the entire group, but one was not able to definitely attribute this to any fault in suture technic. Microscopic sections of the knots and sections of the ligatures were also studied. Details are to be found in the captions to Figure 5.

Clinical Experiences—During the past 16 years, the author has personally tied the more important knots in a selected series of abdominal cases which include 25 rectus or midline wounds, 75 McBurney incisions and 50 incisions for inguinal hernia. The patients were operated upon in six different hospitals and their progress observed from one to five years after operation. The knots used were square ones consisting of three loops or throws (Fig. 2). The first throw was tied in the right hand or clockwise direction with particular care to produce tension by pulling the hands in a plane parallel to the structure being ligated. The second throw of the knot was tied counter-clockwise (left hand throw) and the loop drawn only fairly tight. The third loop of the knot was then tied as in the first, *i. e.*, clockwise direction with tension estimated to be approximate to the amount used in the first throw. Thus the first and third throws are tied in the corresponding direction of the twisted material. In the first loop of the knot after crossing the ligature, the catgut was spun clockwise in the right hand and counter-clockwise in the left hand as it was being drawn taut. The rotation of the catgut between the thumb and index finger as mentioned above prevents to a certain extent the unwinding of the twist in the material when the first throw of the knot has been applied. The loss of twist at the point near the knot no doubt is of considerable importance in the process of disintegration. It has been the common experience of all to see the continuity of the material broken at this point.

In the 100 cases of rectus, midline and McBurney wounds there were no postoperative herniae. In the 50 hernial wounds, two recurrences were found: one, subsequent to a secondary infection, the other, a latent recurrence following a fall. Number 1 chromic catgut, of various manufacturers, was used in practically all of the 150 cases.

It is to be admitted that the writer has had the usual number of post-operative abdominal herniae secondary to drainage in peritoneal infection. However, since the publication⁶ of the work (1924) on drainage of abdominal

wounds, no herniae have developed in those cases where that described procedure has been used. During the past 16 years, the writer has had no cases of postoperative disruption of abdominal wounds in noninfected cases. This may be attributed to the careful application of catgut and to the particular attention to exact detail in tying knots.

SUMMARY

(1) The conventional method of spinning catgut suture material is the right hand or clockwise procedure.

(2) Review of the literature shows varied and divergent results in regard to hydrolysis or absorption of catgut.

(3) Very little information is to be found on the absorption of catgut in terms of the tensile strength.

(4) Only one article on thorough experimental work pertaining to catgut knots was to be found (Taylor,¹⁷ 1938).

(5) Experimental and clinical data are presented to show that the loss of the twist in the catgut suture material is an important factor to be considered in the reliability and the absorption of the material.

(6) The loss of twist in catgut suture material exposes more surfaces of the suture or ligature to the influence of the tissue juices.

(7) Square or reef knots may be tied with the first throw of the knot applied either in the right hand (clockwise) or left hand (counter-clockwise) direction.

BIBLIOGRAPHY

- ¹ Booth, A. W. The Preparation of Catgut. *Therap. Gaz.*, 10, 810, 1894.
- ² Bulloch, W., Lampitt, L. H., and Bushill, J. H. The Preparation of Catgut for Surgical Use. Medical Research Council, Special Report Series, No. 138, London. His Majesty's Stationery Office.
- ³ Callender, G. W. A Femoral Artery Tied with Catgut and Some Experiments with Catgut Ligatures. *Trans. Path. Soc., London*, 25, 102, 1874.
- ⁴ Claudius, M. Undersøgelse over Jodkatgut et indlaeg i Katgutspørgemaalet. *Kjøbenh. B. Borgen*, 94, 8°, 1906.
- ⁵ Goris, A., et Rolland, P. Sur resorption du catgut. *Ann. de l'Inst. Pasteur, Paris*, 31, 269, 3 pl., 1917.
- ⁶ Horine, C. F. Aseptic Technic for the Resection of Intestine, Blind End-to-End Anastomosis with the Release of Purse-String Sutures after the Anastomosis Is Complete. *ANNALS OF SURGERY*, 76, 745, 1922.
- Idem*. Aseptic Technic for the Resection of Intestine, Report of Three Additional Cases. *ANNALS OF SURGERY*, 79, 100, 1924.
- ⁷ Horine, C. F. The Prevention of Acute Intestinal Obstruction, Analysis of 100 Cases. *ANNALS OF SURGERY*, 80, 42, 1924.
- ⁸ Howes, E. L. Factors Determining the Loss of Strength of Catgut When Embedded in the Tissue. *J. A. M. A.*, 90, 530, 1928.
- Idem*. The Strength of Wounds Sutured with Catgut and Silk. *Surg., Gynec. and Obstet.*, 57, 309, 1933.
- ⁹ Howes, E. L., and Harvey, S. C. The Strength of Healing Wounds in Relation to Holding Strength of the Catgut Suture. *New Eng. Med. Jour.*, 200, 1285, 1929.

- Idem* Tissue Response to Catgut Absorption, Silk and Wound Healing, Correlation with Tensile Strength Internat Jour Med and Surg, 43, 225, 1930
- Idem* Clinical Significance of Experimental Studies in Wound Healing ANNALS OF SURGERY, 102, 941, 1935
- ¹⁰ Howes, E L, Sooy, J W, and Harvey, S C The Healing of Wounds as Determined by Their Tensile Strength J A M A, 92, 42, 1929
- ¹¹ Ilyin, A J The Rapidity of Absorption of Catgut by Various Tissues Russk Khir Arkh, 24, 815, 1908
- ¹² Jenkins, J P A Clinical Study of Catgut in Relation to Abdominal Wound Disruption Surg, Gynec and Obstet, 64, 648, 1937
- ¹³ Kraissl, C J, and Meleney, F L A Method for Determining Time of Catgut Digestion *In Vitro* Surg, Gynec and Obstet, 59, 161, 1934
- ¹⁴ Macewen, W Clinical Lectures on Some Points Connected with the Treatment of Wounds Brit Med Jour, London, 1, 150, 1881
- ¹⁵ Phillips, W G The Absorption and Tensile Strength of Certain Absorbable Animal Ligatures A Preliminary Report J A M A, 62, 1306, 1914
- ¹⁶ Rhodes, J E, Hottenstein, H R, and Hudson, I F The Decline in the Strength of Catgut after Exposure to Living Tissues Arch Surg, 34, 377, 1937
- ¹⁷ Taylor, F W Surgical Knots ANNALS OF SURGERY, 107, 458, 1938

ANNOUNCEMENT OF A STUDY TO EVALUATE ORIGINAL SEROLOGIC TESTS FOR SYPHILIS

U S PUBLIC HEALTH SERVICE
WASHINGTON, D C

MORE than five years ago, the Committee on Evaluation of Serodiagnostic Tests for Syphilis, in cooperation with the United States Public Health Service, conducted a study to evaluate original serologic tests for syphilis, or modifications thereof, in the United States. The results of this study were published shortly after the investigation was completed.¹

Consideration is now being given by the Committee to the organization of a second evaluation study of original serologic tests for syphilis, or modifications thereof, within the next year. If the need for an investigation of this kind seems to justify the cost, invitations will be extended to the authors of such serologic tests who reside in the United States, or who may be able to participate by the designation of a serologist who will represent them in this country. The second evaluation study will be conducted utilizing methods comparable to those employed in the first study.²

Serologists who have an original serologic test for syphilis, or an original modification thereof, and who desire to participate in the second evaluation study, should submit their applications not later than October 1, 1940. The applications must be accompanied by a complete description of the technic of the author's serologic test or modification. All correspondence should be directed to the Surgeon General, United States Public Health Service, Washington, D C.

*Thomas Parran, M D ,
Surgeon General*

REFERENCES

- ¹ Ven Dis Inform, Washington, 16, 189, June, 1935
J A M A, Chicago, 104, 2083, June 8, 1935
² J A M A, Chicago, 103, 1705, December 1, 1934

EDITORIAL ADDRESS

Original typed manuscripts and illustrations submitted to this Journal should be forwarded prepaid, at the author's risk, to the Chairman of the Editorial Board of the ANNALS OF SURGERY

Walter Estell Lee, M D
1833 Pine Street, Philadelphia, Pa

Contributions in a foreign language when accepted will be translated and published in English

Exchanges and Books for Review should be sent to James T Pilcher, M D, Managing Editor, 121 Gates Avenue, Brooklyn, N Y

Subscriptions, advertising and all business communications should be addressed

ANNALS OF SURGERY
227 South Sixth Street, Philadelphia, Pa



TRANSACTIONS OF THE AMERICAN SURGICAL ASSOCIATION

MEETING HELD IN ST LOUIS, MO

MAY 1, 2, 3, 1940

ADDRESS OF THE PRESIDENT

THE CRITICAL LATENT OR LAG PERIOD IN THE HEALING OF WOUNDS*

ALLEN O WHIPPLE, M D

NEW YORK, N Y

THIS GREAT HONOR of election to the presidency of the American Surgical Association is deeply appreciated, especially when I consider the character and ability of my predecessors and the standing and attainment of you, my colleagues, who have conferred upon me this durable distinction

It seems strange that in the more than half century of the life of this Association, 50 years of the greatest advances in the history of surgery, none of the Presidential Addresses have dealt with the subject of wound healing. Was it because it was considered an old, commonplace subject of insufficient interest to surgeons? Rather, I believe, it was because the subject presented many poorly understood biologic factors and controversial points of technic which made those, who had been chosen by their associates to preside over their meetings, hesitate to present such an everyday topic. This makes my temerity the greater in attempting to present a certain phase of the subject before such an experienced and critical group of surgeons.

I have chosen this topic—the lag period or phase of adjustment in wound healing—because it is the critical period of repair in which is initiated the sequence of definite processes leading to the fibroplastic fusion of the wound surfaces, and because this sequence may be helped or hindered by the surgeon in his management of the patient and of the wound.

* Delivered before the American Surgical Association, May 1, 1940, St Louis, Mo

Wound repair is preeminently a surgical problem. As surgeons, we treat accidental wounds—and we make wounds. We should, therefore, be particularly interested in their optimum repair and the part we may take in accelerating or retarding the reparative process. As teachers in medical schools, and as senior surgeons in leading hospitals, our example and our interest in wound repair play a major part in the sound basic training and apprenticeship of the younger attending surgeons and residents who will follow us in handing on the fine traditions of American surgery.

Wound healing is a composite biologic phenomenon which conforms, in general, to the laws of growth. The processes involved interact with one another, but each shows quantitative variations depending upon the tissue involved in relation to the conditions present in the wound. The three most important processes involved in wound repair are: (1) The amoeboid movement, (2) the mitotic proliferation, and (3) the maturation of the cells engaged in the fusion of the wound surfaces. But before amoeboid movement and mitotic proliferation can progress, certain activities in the wound space and the bordering tissues of the wound surfaces must first be completed. These activities take place during the latent or lag period. Their extent and relative interaction are determined by both local and systemic conditions.

The local factors are (1) The amount of killed or damaged tissue in the wound surfaces, (2) the vascularity of the tissues involved. The more abundant the capillary bed the more rapid the repair, (3) the integrity of the blood flow to the damaged tissue. This determines the nutrition and viability or the necrosis of the tissues bordering on the wound surfaces, (4) the amount and character of the exudate in the wound space and in the tissues bordering the wound, (5) the number and character of infectious organisms in the wound space and the bordering tissues, (6) the number and character of foreign bodies to be extruded or encapsulated.

The systemic conditions which determine the duration of the lag period and which have a profound influence on one or more of the local factors are (1) The age of the tissues, whether they are adolescent, normal adult or senescent and degenerated, (2) the state of normal hydration. Dehydration or overhydration of the tissues is determined by the water, electrolyte and protein balance in the blood, and may profoundly alter the conditions in the wound surfaces and the wound space contents, (3) normal nutritional balance. Protein deficiency retards, high protein diet accelerates wound healing. Fat heals slowly. A high fat diet prolongs the repair of wounds, (4) vitamin balance. It has been definitely shown that both C avitaminosis and C vitamin deficiency prolong the lag period because of the essential rôle of vitamin C in the formation of intercellular substance and the maturation of the fibroblast and the transformation of fibrous to collagen fibers, (5) the state of the general circulation and blood picture. Poor circulation and severe anemia definitely alter or delay wound healing.

In the study of wound healing the least complicated sequence of reparative processes is seen in the cleanly incised wound made and closed with

the strictest aseptic, atraumatic and hemostatic technic. For this reason such a wound is of the greatest interest to both biologist and surgeon. In such a wound the lag period of four days is uniform provided there are none of the systemic deleterious factors present. The initial escape of blood and plasma is minimal, the formation of a fibrin mesh from the plasma is not unduly delayed by the necessity of elimination of much dead tissue by autolysis, heterolysis, and phagocytosis, and the excessive exudate of bacterial and foreign body reaction does not widely separate the wound surfaces. The quiescent period of agglutination of wound surfaces by a thin layer of fibrin in such a wound is short.

Whether there is a definite initiation of the ameboid movement of new connective tissue cells by growth stimulating substance elaborated by freshly damaged cells is not yet proven. Some 20 such activating factors have been described. Certainly, in tissue cultures it has been shown by Canel and his associates¹ that embryonic tissue juice stimulates cell growth. Products of cell destruction are considered by many workers to have a stimulating effect on the reparative process. Baker² considers glutathione and hemoglobin to be the stimulating substances in fibroblastic proliferation. Hammett³ claims the sulphhydryl radical as the essential effective stimulus to cell proliferation in wound repair. Von Gaza⁴ believes that the inadequacy of oxygen supply and other nutritive substances in the ischemic border or plane in wounds leads to a tissue hunger which initiates cell division and ameboid activity of fibroblasts and endothelial buds.

The destructive or lytic phase by which dead tissue is removed is succeeded by ameboid movement into the fibrinous zone of fibroblasts, derived not from the adjacent fixed tissues but from the wandering connective tissue cells, fibroblasts, polyblasts and histocytes. At this time mitotic proliferation of these mesenchymal connective tissue cells is accelerated.

Leo Loeb⁵ has emphasized the importance of two processes in this stage of the lag period connected with the ameboid movement and proliferation of the invading fibroblasts. The first is the phenomenon of stereotropic response of growing cells to surfaces. Fibroblasts in contact with fibrin strands or fibrils have a strong tendency to elongate and grow along the fibrils, just as epithelial cells show ameboid movement along plane surfaces of granulation tissue or beneath the scab. The second reaction is a centrifugal force which directs the cells away from their own tissue and into the plasma mass in the wound space. This induces various kinds of cells, including fibroblasts, to move into blood clot in a fan-like manner to take part in the organization of the clot. Similarly, endothelial buds show a centrifugal growth into the organizing fibrin with a spread of the vascular bed and thus enter into the formation of granulation tissue.

These reactions may be considered essentially the reactions of cells to foreign bodies. Surface changes in cells lead to agglutination and occur in response to the stimuli which may well be due to differences in electric poten-

tial Ameboid movements, phagocytosis and giant cell formation represent different manifestations and degrees of the same reactions

With the maturation of the fibroblasts and their elongation along the fibrin fibrils uniting the wound surfaces, and the development of collagen fibers from the elongated fibroblasts, there takes place the change from the lag period of no appreciable tensile strength in the wound to the second phase of wound healing, the period of fibroplasia, characterized by a sudden and rapid increase in tensile strength. Harvey and Howes,⁶ in their many contributions to the study of the tensile strength of wound repair, have established wound healing on a firm physiologic basis and have given surgery the soundest and the simplest rationale for the management and technic of wound repair. For the tensile strength of the wound is what really matters, both in the rapidity and permanency of its accomplishment

From the practical surgical standpoint the lag period is the interval between the receipt of the wound and the beginning of tensile strength, during which time the wound surfaces have to be held together by mechanical means, by sutures, by splinting, or by constantly maintained pressure. These measures must be carried out with the least damage to the wound surfaces and bordering tissues, maintenance of maximum nutrition, adequate blood supply, minimum foreign body reaction, and maintenance of rest by immobilization of the damaged tissues. This is the period of wound repair where the surgeon can contribute constructively or destructively by the intelligent employment of his art

It is in his efforts to insure and maintain wound repair that the thoughtless surgeon makes his most common mistake by suturing the wound edges and individual layers too tightly—and with suture material out of all proportion to the holding strength of the tissues. Anyone who has studied the vascular bed of the peritoneum or of muscle by micromanipulation technic is aware of the minute amount of pressure necessary to obstruct or obliterate the blood flow in the capillaries and the arteriovenous channels. Undue tension in the sutures will cause wide zones of anemic, even ischemic tissue, thus prolonging the lag period, by increasing the lytic process in the wound

In no field of surgery is this factor of tension ischemia better illustrated than in intestinal anastomosis. Fortunately the peritoneal layer, because of its very rich capillary bed, is the surgeons', as well as the patients', best friend. The recent introduction of the Miller-Abbott tube as a preoperative measure in resections of the small intestine and in right-sided colectomies, has reduced the mortality following these major procedures 50 per cent—all due to the fact that the bowel is deflated before and after the anastomosis, thus removing that ominous factor of tension

It is in the understanding of the systemic factors of wound healing that the most recent advances have been made. In this field the science of surgery adds immeasurably to the art of wound repair. Attention is called to these factors outside of the wound in the management of repair

(1) *Age Influence*—Clinically, it has always been known that wounds

heal more rapidly and firmly in the young than in the old. DuNouy⁷ demonstrated a faster rate of wound healing in young animals, and Howes and Harvey⁸ found in young rats an earlier onset of fibroplasia, a lessened retardation, and an earlier termination of the process. It becomes the more important to maintain tissue nutrition and avoid the local deleterious factors of infection and foreign body reaction in repairing wounds in the old patient and in senescent, poorly nourished tissue.

(2) *Normal Fluid Electrolyte and Protein Balance*—The symposium that is to follow this address is evidence of the interest of the surgeon of to-day in this exceedingly important factor in tissue metabolism and tissue repair. Overhydration may cause as serious disturbance in wound healing and prolongation of the lag period as dehydration, for edema definitely delays the onset of fibroplasia. Extreme degrees of dehydration, as seen in prolonged or severe fluid and electrolyte loss, deplete intercellular fluid and may disturb the intracellular salt and fluid balance, which will threaten not only local wound healing but the individual himself. Methods, now perfected, for determining fluid and salt balance are essential in following the course of patients operated upon after, or with severe fluid loss from hemorrhage, fistulae or prolonged increased temperature. These same determinations of hematocrit and plasma specific gravity and acid-base ratio should be determined in order to avoid overhydration.

Protein deficiency, seen in hypoproteinemia, may be caused by prolonged protein starvation, or protein loss following hemorrhage, inflammatory exudate or fistula drainage. Hypoproteinemia, because of the reduced large molecular content of the blood, results in fluid loss from the capillary bed into the intercellular spaces and intercellular edema. Ravdin⁹ and his associates have demonstrated abdominal wound disruption in over 70 per cent of dogs operated upon in the presence of hypoproteinemia. The wound edges in periods after wound closure were soggy with edema and, in some instances, showed no evidence of fibroplasia at the seventh and fourteenth days. The wound surfaces were held together only by the silk sutures employed in the closure. In wounds sutured with catgut only the knots were left, in others no remnants of catgut could be found. Unfortunately, we have all noted this same picture in disrupted abdominal wounds in depleted patients. It is essential to determine the blood protein level in the cachectic or depleted individual before operation and to precede surgery with measures directed toward raising the protein content to normal. Plasma transfusions and, whenever possible, because more effective, the Miller-Abbott tube should be employed for administering split-protein products which the patient cannot take by mouth.

(3) *Normal Nutritional Balance*—Protein maintenance, aside from its effect on intercellular fluid, is necessary to provide cellular nutrition. The manner in which tissues obtain their nitrogen and build up their new protoplasm still remains a mystery, but the fact is that tissues in the wound require protein as well as the tissues elsewhere. Clark¹⁰ was the first to study the

effect of diet on the healing wound. It is interesting that the type of diet employed influenced the total period of healing proportionately as it affected the latent period—a high protein diet eliminated the lag period, whereas a high fat diet prolonged it to six days.

Heimannsdorfer¹¹ claimed that an acid diet excited a marked effect in hastening wound healing, on the ground that bacterial growth is inhibited, whereas on an alkaline diet the wound swarmed with bacteria, and was accompanied with a foul exudate. Reimers and Winkler¹² produced an acidosis in dogs, through the administration of ammonium chloride, and found a definite shortening of the period of wound healing.

(4) *Vitamin Balance*—Of the enormous amount of research undertaken to establish the rôle of the many vitamins in tissue metabolism, two vitamins have emerged as being of special significance in relation to wound healing.

Vitamin C—It is now well-established that intercellular substance in general, and especially in the capillary bed, and the collagen of all fibrous tissue require ascorbic acid for their production and maintenance. Hojer¹³ found an atrophy of connective tissue in scorbutic guinea-pigs, and was the first to call attention to a general deficiency in collagen formation. Wolbach,¹⁴ in this country, has confirmed these findings and has shown that ascorbic acid is intimately concerned with the synthesis and maintenance of intercellular supporting substance. This is of special significance in the capillary bed where lack of or deficient intercellular cement substance results in hemorrhage into the wound space and in the bordering tissues prolonging the lag period. Lanman and Ingalls,¹⁵ and Taffel and Harvey¹⁶ have shown by animal experiments that not only C avitaminosis but partial vitamin C deficiency causes a prolongation of the lag period and delays the return of tensile strength because of insufficient collagen fiber formation.

Methods of determining vitamin C in the blood are still inaccurate and are being refined. This accounts for the conflicting reports by workers in this field. There is still some uncertainty as to the length of time man can remain C-vitamin depleted before showing signs of scurvy, but the rôle of vitamin C in the formation of intercellular substance and collagen seems definitely established.

It is the partially deficient vitamin C state that is seldom suspected or anticipated. Holman¹⁷ found that 44 per cent of the "run of the mill" patients in the Stanford-Lane Surgical Clinic wards were deficient in vitamin C—and this in the land of the Sunkist orange. Of 34 patients admitted to a London hospital,¹⁸ 14 showed evidence of vitamin C deficiency. All those above 70 years of age showed relative deficiency. It was also found that patients admitted for peptic ulcer therapy showed no vitamin C deficiency, but four days of a strict ulcer dietary regimen resulted in a deficiency of vitamin C. This is a most important consideration in the preparation of patients, with ulcer or carcinoma, who have been on rigid diets, such as the Sippy regimen. They should regularly be tested for blood vitamin C content and not operated upon until the deficiency is corrected.

Vitamin K—This more recently studied vitamin has a very essential rôle in the control of hemorrhage in relation to prothrombin deficiency. Of special significance, and life-saving, is the employment of vitamin K with bile salts in jaundiced or acholic patients. This is so well-known now that it is generally administered in all clinics. Jaundice is the warning signal to the surgeon for vitamin K therapy.

(5) *Circulatory Imbalance and Anemia*—With present day methods for determining cardiac output and myocardial efficiency, the cardiovascular competence can be definitely determined before operation, and with direct donor transfusion or bank blood transfusion there is no excuse for operating upon markedly anemic patients. Hematocrit and blood plasma determinations have added tremendously to the scientific care of anemic and depleted patients before, during, and after operation.

The lag period is universal as a growth phenomenon. It is seen in plant, fungous and bacterial growth, as well as in the growth of cells in the repair of wounds. Because it is the interval during which the wound surfaces are held together by measures other than the natural body tissues and provided by surgical technics, this period is the surgeon's concern. Another most important rôle of the surgeon is in keeping the wound clean. When infection gains a footing the destructive stage of the lag period is prolonged or made to recur, with a corresponding delay in the fibroplastic phase. The destructive phase of the lag period due to infection is the dangerous period. In the presence of certain bacteria, such as the *Beta* hemolytic streptococcus or the colon group, the newer sulphonamide group of chemotherapeutic drugs prevent or shorten wound infection before the limiting pyogenic membrane prevents the diffusion of the drug by the blood stream. Local application of the crystals of these drugs promises real results in the control of bacteria in areas walled-off by pyogenic membrane or fibrinopurulent adhesions. These drugs *per se* do not hasten but rather seem to delay normal primary wound healing according to Bicker and Graham.¹⁰

Every true surgeon cannot help being interested in wound healing. The problems presented in the repair and management of the wound call for all the science as well as the art of surgery, especially in relation to the critical lag period of wound healing. The art of surgery, based upon the necessity for preventing tissue damage and foreign body reaction, consists of the aseptic and hemastatic use of sharp knife dissection, delicate instruments and fine suture and ligature material that is not more than twice as strong as the holding tissues. We can do this much at least in not making the lag period the dangerous period in wound healing.

REFERENCES

- ¹ Carrel, A. Jour Exper Med, 15, 516, 1912
- ² Baker, L. E. Jour Exper Med, 49, 163, 1929
- ³ Hammett, F. S. Proc Am Phil Soc, 68, 151, 1929
- ⁴ von Gaza, W. Beitr z klin Chir, 110, 347, 1918
- ⁵ Loeb, L. Jour Med Res, 41, 247, 1920

- ⁶ Harvey, S C, and Howes, E L ANNALS OF SURGERY, 91, 641, 1930
Howes, E L, and Harvey, S C Yale Jour, Biol and Med, 2, 285, 1930
- ⁷ DuNouy, P L Compt-rend Soc de biol, 109, 1227, 1932
- ⁸ Howes, E L, and Harvey, S C Jour Exper Med, 55, 577, 1932
- ⁹ Thompson, W D, Ravdin, I S, and Frank, I L Arch Surg, 36, 500, 1938
- ¹⁰ Clark, A H Johns Hopkins Hosp Bull, 30, 117, 1919
- ¹¹ Herrmannsdorfer, A Deutsch Ztschr f Chir, 200, 534, 1927
- ¹² Reimers, C, and Winkler, H Deutsch Ztschr f Chir, 241, 313, 1933
- ¹³ Hojer, J A Acta Paediat, 3, Supp 8, 1924
- ¹⁴ Wolbach, S B Am Jour Path, 9, 689, 1933
Idem J A M A, 108, 7, 1937
- ¹⁵ Lanman, T H, and Ingalls, F H ANNALS OF SURGERY, 105, 616, 1937
- ¹⁶ Taffel, M, and Harvey, S C Proc Soc Exper Biol and Med, 38, 515, 1938
- ¹⁷ Holman, E Surg, Gynec and Obstet, 70, 261, 1940
- ¹⁸ Holman, E *Loc cit*
- ¹⁹ ✓ Bricker, E M, and Graham, E A J A M A, 112, 2593, 1939

A most comprehensive and discriminating review of the subject "Wound Healing," including a very comprehensive bibliography, has been written by Leslie B Arey, which is to be found in Physiol Rev, 16, 327-406, July, 1936.

SYMPOSIUM ON FLUID AND ELECTROLYTE NEEDS OF THE SURGICAL PATIENT

Presented Before

THE AMERICAN SURGICAL ASSOCIATION

St Louis, Mo, May 1, 2, 3, 1940

THE STRUCTURE OF THE BLOOD IN RELATION TO SURGICAL PROBLEMS

JOHN P PETERS, M D, New Haven, Conn

THE PRESERVATION OF BLOOD

DAVID C BULL, M D, and CHARLES R DREW, M D, New York, N Y

STUDIES OF BLOOD PRESERVATION THE STABILITY OF PLASMA PROTEINS

JOHN SCUDDER, M D, New York, N Y

SODIUM CHLORIDE METABOLISM OF SURGICAL PATIENTS

WALTER G MADDOCK, M D, and FREDERICK A COLLER, M D, Ann Arbor, Mich

FLUID, SALT AND NUTRITIONAL BALANCE IN PATIENTS WITH INTESTINAL SUCTION DRAINAGE

GROVER C PENBERTHY, M D, J LOGAN IRVING, M D, and R MAYO TENERY, M D,
Detroit, Mich

Discussions by

WALTMAN WALTERS, M D

OWEN H WANGENSTEEN, M D

A CLINICAL STUDY OF THE PLASMA VOLUME IN ACUTE INTESTINAL OBSTRUCTION

JACOB FINE, M D, ALFRED HURWITZ, M D, and JEROME MARK, M D, Boston, Mass

PLASMA LOSS IN SEVERE DEHYDRATION, SHOCK AND OTHER CONDITIONS AS AFFECTED BY THERAPY

A S MINOT, PH D, and ALFRED BLALOCK, M D, Nashville, Tenn

PHYSIOLOGIC FACTORS REGULATING THE LEVEL OF THE PLASMA PROTHROMBIN

JONATHAN E RHOADS, M D, Philadelphia, Pa

HYPOPROTEINEMIA AND ITS RELATION TO SURGICAL PROBLEMS

I S RAVDIN, M D, Philadelphia, Pa

FLUID AND NUTRITIONAL MAINTENANCE BY THE USE OF AN INTESTINAL TUBE

W OSLER ABBOTT, M D, Philadelphia, Pa

PARENTERAL REPLACEMENT OF PROTEIN WITH THE AMINO-ACIDS OF HYDROLYZED CASEIN

ROBERT ELMAN, M D St Louis, Mo

THE RELATION OF PROPER PREPARATION OF SOLUTIONS FOR INTRAVENOUS THERAPY TO ALLERGIC AND FEVER REACTIONS

CARL W WALTFR, M D, Boston, Mass

Discussions by

DALLAS B PHFMISTER M D

J SHELTON HORSLEY, M D

DAMON B PLETIFER, M D

WALTER E LEE, M D

WILLIAM DEW ANDRUS, M D

THE STRUCTURE OF THE BLOOD IN RELATION TO SURGICAL PROBLEMS*

JOHN P. PETERS, M.D.

NEW HAVEN, CONN.

I HAVE CHOSEN to discuss some features of the treatment of gastro-intestinal disorders because these present, in the most exaggerated forms, the chief problem of fluid regulation. Before proceeding to particulars, however, I should like to touch upon certain general principles. First, it is reasonable to assume that reparative processes will be favored by measures that will preserve the integrity of both volume and composition of the body fluids.

All the secretions of the gastro-intestinal tract are approximately isotonic with blood serum, that is, they contain approximately equal concentrations of chemical components. Furthermore, in all these secretions, as in the serum, sodium salts predominate. The chief acids in these fluids are chloride and bicarbonate, chloride giving way more and more to bicarbonate in the descent through the alimentary canal. These facts are illustrated in Figure 1. It follows that a liter of gastro-intestinal contents is roughly equivalent, as far as sodium is concerned, to a liter of normal saline. (An exception must be made of acid gastric contents, in which the sodium is partly replaced by the hydrogen ion.) On the whole, it may be roughly stated that secretions lost from the alimentary canal will contain, on the average, about 0.5 to 0.6 per cent of chloride, estimated as sodium chloride.

Fluids introduced into the stomach or intestine rapidly assume a composition which resembles, so far as salts are concerned, that of the native secretions of these viscera. For example, when water enters the stomach or intestine, enough salt is poured into it to make it isotonic with the blood serum and the composition of the salt mixture assumes the electrolyte pattern characteristic of that portion of the alimentary canal in which it happens to be. If, therefore, a liter of water or saltless fluid, introduced into the intestine, is lost by vomiting or through a fistula, it will remove with it approximately the salt from one liter of serum or interstitial fluid. Under these circumstances the salt concentration—and consequently the osmotic pressure—of the body fluids will fall. Within limits, the body reacts on behalf of osmotic pressure by excreting an equivalent amount of water through the kidneys. The administration of water by mouth, under these circumstances, becomes, paradoxically, a dehydrating measure.

The sequence of events can be illustrated by the example of pyloric stenosis, represented diagrammatically in Figure 2. A depicts the pattern of normal serum. The vertical dimension of each column represents the concentration of bases or acids in the serum, while the horizontal dimension represents the volume of fluid within the body in which these are dissolved.

* Read before the American Surgical Association, May 1, 2, 3, 1940, at St. Louis, Mo.

BLOOD IN RELATION TO SURGERY

The figures at the bottom indicate what proportion of the components indicated still remains in the body at each interval For instance, at C 90 per cent

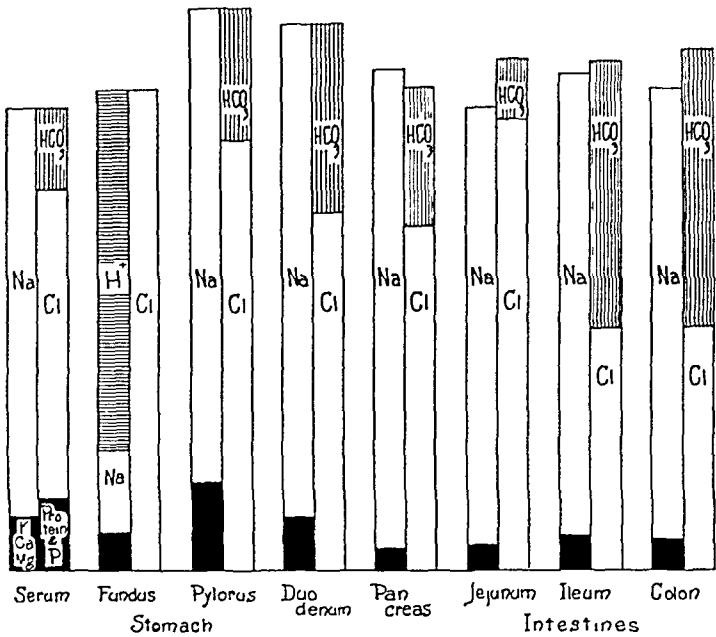


FIG 1—The concentration of bases (cations) and acids (anions) in the serum and gastro intestinal secretions (Compiled from the literature)

of the original body water remains, or 10 per cent has been lost The first event is the loss of chloride as hydrochloric acid in the vomitus, represented

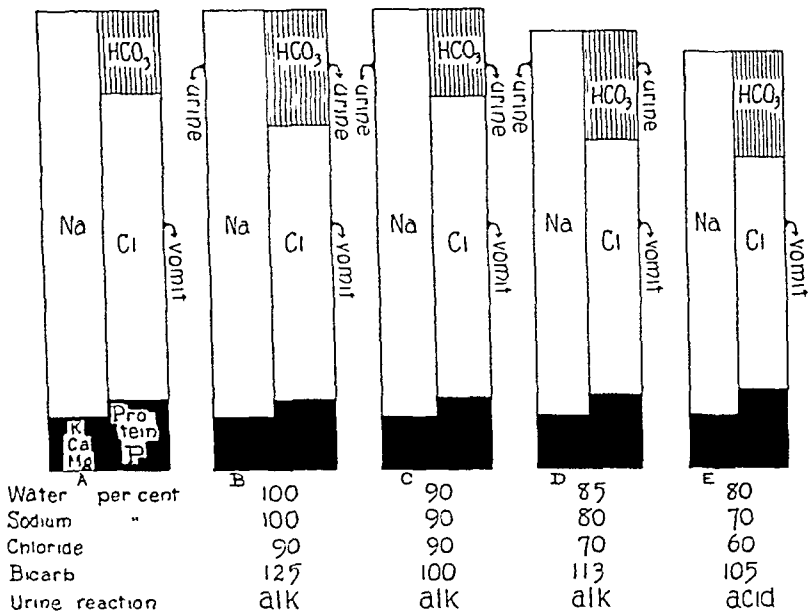


FIG 2—Progressive changes in the chemical pattern of the serum in the vomiting of pyloric obstruction The vertical dimensions of the columns represent concentrations of electrolytes the horizontal dimensions volumes of fluid in the body The figures below the chart indicate the quantities of various components remaining in the body at each stage of the progression, in per cent of the quantities originally present

by the curved arrow on the right of A The sodium formerly combined with the chloride is left behind to form bicarbonate with CO₂ The result is bicar-

bonate excess or alkalosis, represented in B. At this stage, in order to restore a normal serum pattern, excretion of chloride into the urine ceases, the kidney excretes an alkaline urine containing sodium bicarbonate. This mitigates or abolishes the bicarbonate excess. Meanwhile the fluid content of the body has also been reduced. The net effect, pictured in C, is the restoration of the normal composition of the body fluids at the expense of volume (represented by the narrowed columns). Although 10 per cent of the chloride and 10 per cent of sodium have been lost, because of the coincident discharge of 10 per cent of water the pattern appears almost normal. As the vomiting continues, water being taken throughout, a point is reached at which fluid can no longer be spared. The sodium concentration falls, as D shows, since bicarbonate is still sacrificed in the urine in behalf of the acid-base equilibrium to balance chloride lost in the vomitus. If the vomiting proceeds a little further a most anomalous condition ensues. Despite increasing bicarbonate excess the urine suddenly becomes acid. A state has now been reached, illustrated in E, in which no further loss of sodium is tolerated. Acid-base equilibrium is forced to yield to the demands of osmotic equilibrium. In this final stage dehydration, alkalosis, salt depletion and reduction of osmotic pressure are all combined.

4. A similar series of figures could be drawn to illustrate the course of events in severe diarrhea. In this condition bicarbonate is lost in the stools, while chloride is excreted in the urine. The end-result is a deficiency of sodium and bicarbonate with a relative excess of chloride in the depleted body fluids.

The concentrations of sodium, bicarbonate and chloride in the serum give valuable information concerning the severity of vomiting and diarrhea and the extent of the consequent depletion of salt and water. They also provide a check upon the efficacy of therapeutic measures—aimed to overcome these defects. Determination of sodium is too difficult and time consuming for clinical purposes. Since, however, as the figure shows, the sodium salts of serum consist almost entirely of bicarbonate and chloride, its concentration may be estimated with sufficient accuracy from the sum of the concentrations of bicarbonate and chloride.

There is reason to believe that body cells swell when the salt concentration in the body fluids falls, just as red blood cells swell in hypotonic salt solution. Such swelling must seriously impair functional integrity. The most obvious clinical effects of salt depletion and dehydration are shock and failure of renal function, the latter manifesting itself in elevation of the blood non-protein nitrogen. Subcutaneous or intravenous normal saline usually rectifies the disorder, although hypertonic salt is to be preferred when salt depletion is profound. If enough is given to restore the volume of the body fluids and to establish an adequate flow of urine the kidneys will adjust the composition of the body fluids quite readily.

These physiologic facts seem to have certain inescapable implications. First, the alimentary canal is not relieved of work by the introduction of

fluid, and especially water. Second, efforts should be directed to prevention of distention rather than to decompression of stomach or intestines. Third, if only physiologic isotonic solutions are introduced into the alimentary canal, dehydration and salt depletion will be minimized and the need for parenteral fluids will be proportionally diminished.

The best way to test the alimentary canal is to give it nothing to do. Foster¹ and others have shown that if no water or food is given to dogs after ligation of the pylorus, vomiting ceases after a short interval. If only enough saline is given parenterally to replace the fluid and salt lost in the initial vomitus these dogs live just as long as unoperated dogs deprived of food and water. Is there any reason to believe that humans would not behave like these dogs if they were given a chance? In mercury poisoning, although the whole gastro-intestinal tract is ulcerated and irritated to an extreme degree, complete withdrawal of fluids and food by mouth is succeeded almost immediately by cessation of both vomiting and diarrhea.² The term "complete" permits no compromises nor exceptions, not even water in sips or cracked ice.

ILLUSTRATIVE CASE REPORTS

Case 1—No A-1066 A male, age 14, on September 5, had a brain abscess drained. After operation he was treated with sulfapyridine, and was given as much cracked ice as he desired. He vomited with steadily increasing frequency. After three days, although he had received, by infusion and hypodermoclysis, 7,500 cc of fluid containing 300 Gm of glucose and 20 Gm of sodium chloride, he presented the condition pictured in the second column of Figure 3 (the first column represents the pattern of normal serum), namely, completely anuric, pulse 130, blood nonprotein nitrogen 90 mg per cent, serum proteins 93 per cent denoting extreme hemoconcentration. Serum chloride was reduced to 69 mg per cent (30 per cent below normal), bicarbonate was approximately normal. All food and fluids, including ice, by mouth, were stopped and he was given parenterally 6,500 cc of water containing 125 Gm of glucose and 64 Gm of salt. Vomiting and hiccough ceased at once. Within 24 hours the pulse had fallen to a normal rate, the nonprotein nitrogen had dropped to 46 mg per cent and he was voiding freely. Serum chloride and bicarbonate had been restored. At the end of three days, during which he vomited only 10 cc, the nonprotein nitrogen was normal (28 mg per cent), and the serum proteins had fallen to 68 per cent. A liquid diet was given that day and on the next he was able to take a soft diet.

Case 2—No A-60808 A male, age 43, because of hemorrhages, and slow perforation of a gastric ulcer, was subjected to plication of the ulcer and gastro-enterostomy. Two years later after two weeks of increasing pain and vomiting, culminating in hemorrhage, he was readmitted to the hospital with signs indicative of slow perforation again.

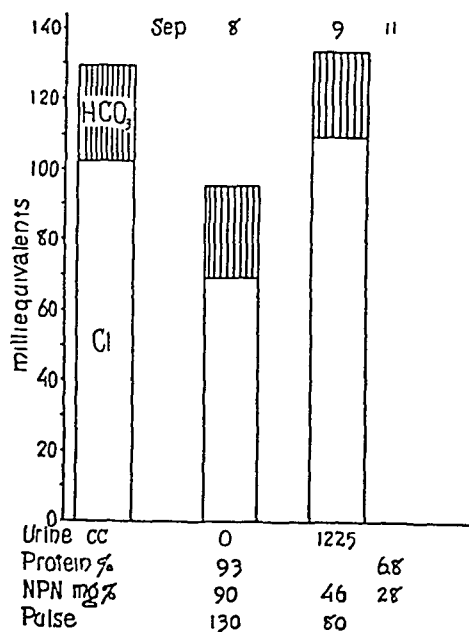


FIG 3—Case 1, No A-1066. The concentrations of bicarbonate and chloride in the serum. The column on the left shows the pattern of normal serum. The figures at the bottom give urine volume, blood nonprotein nitrogen, serum protein and pulse rate.

With nothing by mouth, he vomited only 20 cc in four days, but vomited increasingly when a Sippy dietary regimen was given for three days. When everything was withheld again by mouth he vomited only 30 cc in three days, but once more vomiting returned when he resumed fluids. In each instance, with the cessation of vomiting, other symptoms disappeared. Dehydration was relieved and thirst allayed by parenteral administration of moderate amounts of fluid containing salt. (Needless to say, operation was resorted to when conservative treatment proved ineffective.)

It has been possible, in a few cases, to prove that the vomiting resulting from pyloric obstruction will respond to withdrawal of food and fluids. It may be necessary for the first day or two to empty the stomach if it becomes distended, but there is no apparent advantage in lavaging the stomach, nor in leaving in the stomach a tube or fluid to stimulate secretion. Before any such procedures are instituted the more physiologic process of rest should be given a reasonable trial.

If intubing tubes are used, however, to relieve distention, any fluid introduced into the alimentary canal through them should contain enough salt to make it isotonic with blood serum, especially if the stomach or intestine is obstructed or contains a fistulous opening. To give water by mouth or tube, and saline parenterally, is not equally satisfying. It is next to impossible to establish salt and water equilibrium or a positive balance by this method, even if it were not unduly distressing to the patient. The introduction of water into the obstructed bowel or stomach seems to provoke the excretion of further fluid as well as salt.

Case 3—No A-25125. A female, age 43, who had previously undergone a pelvic operation, entered the hospital with symptoms and signs of intestinal obstruction of four days' duration. Her fluid and salt balance are roughly presented in Table I. Fluids were measured. The salt intake is known. On the basis of other studies, it is estimated that the drainage from the stomach contained chloride equivalent to 0.6 per cent of sodium chloride, while the urine contained no chloride. The chloride excretion is, therefore, probably underestimated. A Wangensteen tube was introduced, and for two days only, small amounts of saline were administered. During the same period 5,500 cc of water containing 27 Gm of salt were administered parenterally. Drainage

TABLE I

Day	Water Intake				Water Out			Water Bal- ance Cc	NaCl		Bal- ance Gm
	Wangen- steen Cc	Oral Cc	Paren- teral Cc	Total Cc	Drain- age Cc	Urine Cc	Total Cc		In Gm	Out Gm	
1	2,100		3,500	5,600	2,100	1,300	3,400	2,200	28	13	15
2	2,350		2,000	4,350	3,300	1,200	4,500	-150	30	20	10
3	1,900	3,400	0	5,300	9,500	550+	10,050	-4,750	17	57	-40
4	2,050	4,350	1,500	7,850	11,200	500	11,700	-3,850	27	67	-40
5	2,100	3,200	3,000	8,300	5,700	1,100	6,800	1,500	37	34	3
6	3,200	1,500	6,500	11,200	8,800	2,300	11,300	100	83	53	30
7	2,250	0	3,000	5,250	2,700	1,450	4,150	1,100	47	16	31
8	1,750	Cracked ice	3,000	4,750+	1,800	1,300	3,100	2,650	43	11	32

through the Wangenstein only slightly exceeded the fluid introduced through the tube. Positive water and salt balances were established, dehydration was alleviated, and urine volume was adequate. The condition seemed so favorable that on the third day parenteral fluids were omitted while nutrient fluids without salt were given by mouth. Although only 3,400 cc of salt free fluid were given this way, drainage from the Wangenstein increased from 3,300 to 9,500 cc—i.e., by 6,200 cc. There was a negative water balance of almost five liters, and an estimated salt deficit of 40 Gm. The urine volume fell sharply. The next day drainage rose to 11 liters. The following day, by the administration of 3,000 cc of saline parenterally, the urine volume rose to one liter, and slight positive balances of water and salt were established. At the end of the five days, serum chloride was only 78 meq (25 per cent below normal, bicarbonate was 37 meq), 10 meq above normal. There was a total salt deficit with alkalosis. The blood non-protein nitrogen was 45 mg per cent (distinctly elevated), the serum proteins were 7.2 per cent (evidence of dehydration in one who was undernourished).

On the following day, by the parenteral injection of an enormous amount of saline (6.5 liters), it was possible to turn the tide. The balance of water was barely positive, if insensible perspiration be ignored. But at what expense! All the fluids that entered the mouth, and most of that given by vein or under the skin, were recovered in the Wangenstein drainage. Contrast this with the next two days. When saltless fluids by mouth were again withdrawn, the drainage diminished at once by 6,100 cc, although the fluid given by mouth and tube was reduced only 2,500 cc. The next day she received only a little cracked ice by mouth. Drainage remained small. At the end of this period the general condition of the patient was greatly improved, urine flow was adequate, blood nonprotein nitrogen normal (26 per cent), the serum proteins had fallen to 6.7 per cent. Serum bicarbonate was normal, chloride distinctly elevated (to 115 meq). This hyperchloremia must not be regarded as a sign that too much chloride has been given, but rather that dehydration has not been entirely overcome. The patient had probably stored little water, if account is taken of the insensible perspiration, but she had retained large quantities of salt. I may add that the intestinal obstruction was overcome without operative intervention.

Table II summarizes the published data³ from a patient with obstruction of the ileum who was decompressed and fed by means of the Abbott-Miller double tube. The authors imply that loss of water and electrolytes was prevented. In actual point of fact, the positive water balance for the four-day period was not more than large enough to provide for the losses that must have been incurred through the urine and insensible perspiration. The drainage from the tube far exceeded the fluid introduced through the tube and washed out all the salt which was given by vein. Less water and salt might have been lost in the drainage if the fluid given by mouth had contained salt. The procedure was particularly unphysiologic in this case, since Dennis⁴ has shown that water has a peculiarly injurious effect upon the mucosa of the ileum.

The following case illustrates a somewhat different phase of the same problem.

Case 4—No. A-75015. A female, age 19, with ulcerative colitis and polyposis of the colon, was admitted with a recurrent perirectal abscess and fecal fistula which necessitated an ileostomy. She was greatly emaciated, weighing less than 80 lbs. All attempts to improve her condition were unavailing because of the amounts of food and fluid which

TABLE II
FOUR DAYS' INTESTINAL OBSTRUCTION
(Abbott and Miller)³

Fluid in		
By mouth	19,525 cc	
By vein	10,930 "	
	<hr/>	
Total	30,455 "	
Drainage	23,400 "	
	<hr/>	
Balance	7,055 "	
Balance per day		1,764 cc
Salt (as NaCl) in		
By mouth	9 7 Gm	
By vein	106 9 "	
	<hr/>	
Total	116 6 "	
Drainage	111 1 "	
	<hr/>	
Balance	5 5 "	
Balance per day		1 4 Gm

escaped through the ileostomy. Moreover, salt depletion could only be prevented by frequent parenteral injection of saline. Finally, without changing her diet, which consisted of high caloric low residue foods, she was given in addition enough 1 to 3 per cent sodium chloride solution to drink to make all the food and fluids which she took isotonic with the blood serum. Within three days the discharge from the ileostomy, which had varied from 1,000 to 1,500 cc daily, fell to from 400 to 800 cc. At the same time serum chloride and bicarbonate became normal. By the end of seven months she weighed 120 lbs., a gain of 40 lbs. There has not yet been an opportunity to repeat this procedure to learn whether it will succeed in other patients with intestinal fistulae. But it seems logical that by making the nutritive fluids which enter an irritable or irritated intestine isotonic with serum by means of sodium chloride, hypersecretion and hyperactivity may be reduced and absorption promoted.

CONCLUSION

Distention and vomiting, either before or after operation, may often be allayed or checked by resting the gastro-intestinal tract as completely as possible. Complete rest is most easily achieved by withholding all food and fluids by mouth. If drainage by tube or lavage is instituted because this course or the courage of the physician fails, care should be taken that as little fluid as possible is introduced and that all food or fluid given by mouth or through the tube contains enough salt to make it isotonic with blood serum. This allays secretory and motor activity of the gastro-intestinal tract and mitigates dehydration and salt depletion. If the sum of bicarbonate plus chloride in the serum is reduced, saline should be administered parenterally to restore the fluid and salt content of the body. Glucose may be added to the intravenous saline to provide some nutrition and to reduce protein metabolism. It is unnecessary, however, under these circumstances, to administer large amounts

of fluid parenterally Only enough is required to establish an adequate volume of urine The patient who is excreting 1,000 to 1,500 cc of urine daily is seldom a subject for anxiety

REFERENCES

- ¹ Foster, W C Acute Intestinal Obstruction The Correlation of Recent Experimental Studies and Clinical Applications J A M A , 91, 1523, 1928
- ² Peters, J P, Eisenman, A J, and Kydd, D M Mercury Poisoning Am Jour Med Sci, 185, 149, 1933
- ³ Abbott, W O, and Miller, T G The Diagnostic and Therapeutic Value of Intestinal Intubation in Intestinal Obstruction Trans Am Clin Climatol Soc, 1939
- ⁴ Dennis, C Injury to the Ileal Mucosa by Contact with Distilled Water Am Jour Physiol, 127, 171, 1940

THE PRESERVATION OF BLOOD

DAVID C BULL, M D ,

AND

CHARLES R DREW, M D

NEW YORK, N Y

FROM THE DEPARTMENT OF SURGERY COLLEGE OF PHYSICIANS AND SURGEONS COLUMBIA UNIVERSITY AND THE
PRESBYTERIAN HOSPITAL NEW YORK N Y

WHEN THE PRESBYTERIAN HOSPITAL was considering the establishment of a Blood Bank, there was a demand for data as to what might be expected of preserved blood. It was appreciated that while the ultimate verdict would come from the clinical experience of its use, something of its potential dangers and benefits could be learned by preliminary work in the laboratory. Studies were, therefore, undertaken to find out what changes take place in preserved blood and the best methods of preserving it. This communication will summarize some of the findings but will of necessity omit description of methods, calculations, and other details.

To follow the deterioration of the cells, complete blood counts were made daily on blood preserved in a refrigerator at 4°C , with heparin as the anti-coagulant. A similar series was made on citrated blood. The red cell counts varied, of course, but their mean remained about the same for 30 days in the heparinized blood. In citrated blood there was little change during the first 15 days, then a slow loss of from one to one and one-half million cells by the end of the month. According to Ponder, this loss is unimportant from a functional standpoint, as the capacity of the stored blood to carry oxygen remains unimpaired. The hemoglobin level remained constant, although increasing amounts of it up to 25 per cent were to be found in the plasma.

The mean cell diameter of the red cells steadily decreases from a base value of 7.6 to 5.8 microns at 35 days. The late loss could be due to escape of hemoglobin but this cannot account for the shrinkage of the first week which must depend upon salt and water loss.

Philip Levine² has submitted some interesting data on the length of life of a transfused red cell in the recipient. Identifying the donor cells in the patient by means of the group specific factors M and N, he found that cells stored 3, 10, or 14 days survived for 80, 60, or 20 days, respectively, as compared with cells of fresh blood, which lived over 95 days.

Volume index also decreased progressively—partly, perhaps from the disappearance of white blood cells but mostly from the shrinkage in size of red cells.

The white blood corpuscle total count fell 50 per cent during the first 24 hours, and by the sixteenth day the cells remained only as smudges or amorphous masses. Polymorphonuclear leukocytes changed earliest and disinte-

* Read before the American Surgical Association, St. Louis, Mo., May 1, 2, 3, 1940.

grated most rapidly, but eosinophils and basophils were recognized distinctly as late as the thirty-fifth day

The thrombocyte count fell rapidly to a low level, near which it remained for 15 days. The platelets of blood preserved in citrate solution had a slightly slower initial fall. Determinations of erythrocyte fragility gave poor end-points. It was clear, however, that cells on the tenth day were less resistant than on the first, and still less resistant on the thirtieth.

With these data in mind it is apparent that the red cells of preserved blood can be depended upon to function satisfactorily. To transfuse stored blood for the sake of its white cells or platelets, however, would be a questionable procedure. If we think of the immune factors of blood as being associated with them then the use of fresh blood for infection would be more logical.

The prothrombin percentage, as measured by the Quick method, after a prompt initial fall remains at 50 for a long period. In many cases this amount would be inadequate.

Of the several electrolytes of the blood, potassium is important as the chief mineral base of the red cells, in the serum, however, only one-twentieth of the amount in the cells is found. As has been observed before plasma standing in contact with cells tends to be enriched with cell potassium. On measuring this diffusion process it was found that the rise of plasma potassium begins immediately the blood is withdrawn, continues at a rapid rate for the first few days, and then more slowly until equilibrium is established. This does not depend upon contamination.

Various preservatives modify the time at which hemolysis begins, and one (Peyton-Rous mixture) actually prevents it. But none of those recommended prevents potassium diffusion. The best record was made by a mixture of 0.3 Gm of sodium citrate per 100 cc. The difference in rates at which cells lose potassium and hemoglobin shows that the latter is not a very sensitive criterion of cell deterioration. Nearly one-half the potassium had escaped from the cell before any of the larger hemoglobin molecules were lost. There is a real increase of plasma potassium as the result of shaking. In fresh blood this is not as pronounced as it is a few days later. Unavoidable transportation of preserved blood should be undertaken immediately rather than when it has become several days old.

While the material of the container was not proved to be of importance the shape exerts a definite effect. Blood in an Erlenmeyer flask, for example, shows a more rapid rise in plasma potassium than blood in a test tube, in fact the rate of potassium diffusion varies as the diameter of the area where cells and plasma are in contact.

Investigation of placental blood by similar methods revealed that potassium leaves the cells at much the same rate. Another similarity was the superiority of an 0.31 per cent sodium citrate solution over the Russian citrate compound as a preservative. Judged by their rate of potassium loss, cells of placental blood deteriorate about as do adult cells.

Our interest in potassium was not purely as an index of loss of vitality of

red cells, but also for its possible toxicity. The intravenous minimum lethal dose of potassium for man is not known, and the acceptance of animal tolerance as a guarantee of safety is admittedly fallacious unless a comfortable margin of safety is provided. By analogy, then, three to five liters of blood with plasma containing 100 mg per cent could cause the death of a healthy adult. However, animal tolerance for a potassium infusion is increased many times by administering it slowly. It is unlikely that so much blood would be infused except very slowly as a drip, and improbable that any harm would result.

In patients whose excretion is handicapped or whose serum potassium is already high, care in the use of aged blood is advisable. Particularly in hemorrhage and shock, where the tendency is to transfuse large amounts rapidly, one should use caution on fresh blood.

The higher values of plasma potassium in cadaver blood are striking. At the time of collection it is found at levels found in preserved blood on the fifth day. This could be due in part to the disease which produced death. Another factor is temperature. Diffusion of potassium is much more rapid at 38° than at 4° C, and a cadaver is not chilled as suddenly as is blood under the usual conditions of preservation. A further possibility is the formation of ammonia from breaking down of body proteins. Ammonia could increase cell permeability, as it does in certain plant cells.

Ammonia nitrogen is found in infinitesimal amounts in normal blood but rises rapidly in the first few minutes of exposure to air. It continues its marked rise for four days, to reach the level of 1 mg per cent, where it remains until the tenth day.

The direction taken by the sodium ion is the opposite of that of potassium, the plasma sodium decreases as potassium rises. Evidently it diffuses from the plasma into the cells.

These changes due to diffusion depend upon the permeability of the cells. The process could be slowed if the increasing permeability of the cells could be retarded. The possibility that ammonia is in some measure responsible for this phenomenon suggests the use of carbon dioxide to slow ammonia production.

Comparison of blood collected under carbon dioxide for changes in potassium, sodium, ammonia-nitrogen, and p_H with a control specimen withdrawn in the air demonstrated that carbon dioxide is effectual in retarding the changes in the concentration of these bases and maintains the p_H nearer neutral.

The plasma calcium content remains constant for nine days even when shaken. Magnesium diffuses into the plasma so slowly that the amount accumulated in nine days is too small to have any toxic effect. Moderate trauma does not materially increase the rate.

Of the anions, the fall of plasma carbonates and chlorides and the rise of phosphates are apparently innocuous.

The statistics of reactions following transfusion cannot be briefly presented because of the necessity of detailed information as to criteria and technic.

However, with these two factors constant, only one difference in the incidence and severity of reaction between fresh citrated and stored citrated blood need be anticipated, namely, jaundice. This is transient and asymptomatic but frequently follows use of blood stored for nine or more days.

The outstanding changes of clinical interest taking place in stored blood are its loss of white blood cells and platelets, its increase in plasma potassium, and decrease in prothrombin. For most purposes it should give results comparable with fresh blood, for infection, prothrombin deficiency, and shock it would be inferior. Intelligently employed during the first week of storage, it need be neither dangerous nor disappointing.

REFERENCES

- ¹ Drew, C. R., Edsall, K., and Scudder, J. *Jour. Lab. and Clin. Med.*, **25**, 240-245, 1939.
- ² Levine, Philip. To be published.
- ³ Scudder, J., Drew, C. R., Corcoran, D., and Bull, D. C. *J. A. M. A.*, **112**, 2263-2271, 1939.
- ⁴ Scudder, J., Corcoran, D., and Drew, C. R. *Surg., Gynec. and Obstet.*, **70**, 48-50, 1940.
- ⁵ Smith, M. E., Tuthill, E., Drew, C. R., and Scudder, J. *Jour. Biol. Chem.*, **133**, 499-501, 1940.

STUDIES IN BLOOD PRESERVATION^{*}

THE STABILITY OF PLASMA PROTEINS

JOHN SCUDDER, M D

NEW YORK, N Y

FROM THE LABORATORIES OF THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH NEW YORK N Y

THE PREPARATION of an artificial fluid medium which could be used for perfusion experiments was suggested by the French physiologist, Le Gallois, in 1812 To-day, the increasing interest in plasma transfusions signifies a nearer approach to this ideal⁵ The advantages of plasma are many It is a more stable system than blood, because of its buffer capacity, it is superior to acacia, glucose, and salt infusions, its ionic content is of physiologic proportions, it contains certain organic substances necessary for maintaining protoplasmic irritability, and, in addition, it possesses proteins which are concerned with innumerable functions of the body economy

In 1871, Bowditch, working in the laboratory of Carl Ludwig, observed the greater efficacy of serum as a perfusion fluid He saw a frog's heart, which had been arrested by salt, revived by serum

Ringer at first disagreed that serum possessed any attribute other than that due to the presence of the salts in balanced proportion Later, however, he admitted that even a frog's heart brought to a standstill by physiologically correct salt solutions could be revived through serum infusions

Both plasma and serum restore the irritability of protoplasm This is not peculiar to the vegetable kingdom (a)[†] but applies also to the heart muscle of both cold (b)[†] and warm (c)[†] blooded animals Other substances share in this restorative action such as milk,³² gastric juice,³² digested peptones,⁷² milk whey,²⁸ egg white,⁷⁶ and gelatin⁷⁶ Wieland,⁹⁸ in 1921, confirmed this action of serum and demonstrated that surface-active agents such as sodium oleate, ether, xylol, camphor, and animal charcoal corrected the hypodynamic state of the excised frog's heart through adsorption of the accumulated metabolic products

This activating substance is soluble in water or dilute alcohol and is organic in nature Heating the plasma or cooking the serum lessens the restorative effect⁸⁵ It is not removed by ether⁷⁶ Its widespread distribution in both the vegetable and animal cells is of provoking interest

To-day, the progressive deterioration of preserved whole blood has become apparent On the other hand, the stability of preserved plasma is now recognized There are certain advantages of plasma⁹³ over whole blood, especially over blood stored too long⁸⁰

* Read before the American Surgical Association, St Louis, Mo, May 1, 2, 3, 1940

† (a) Leached *Nitella* cells⁶⁹

(b) Toad,⁷² frog,^{7 26 32 42 45 52 57 62 70 76 81 85} turtle^{42 62}

(c) Cat,^{27 28 45} dog,^{36 45} rabbit^{36 77}

Ambeison,⁴ in his review of the literature on blood substitutes, has pointed out some of the advantages of plasma

Plasma Is Nonantigenic—The acid proteins of the erythrocyte membrane³⁵ as well as hemoglobin have been shown to be antigenic. For this reason repeated transfusions are at times dangerous. Repeated plasma transfusions have been given without anaphylactic reactions³³. Thus plasma may be safer than blood⁶⁷.

Plasma Is Less Toxic—There have been many untoward reactions with serum. In dogs, the use of concentrated serum has given rise to shock² and to severe chills²⁵. The reactions become graver with the use of heterologous sera^{43 56 75}. In the cat, following such serums a decrease in blood pressure, together with changes in the liver, kidneys, and lungs has been noted⁸. In rabbits, Rous and Wilson⁷⁸ have reported the development of liver necrosis following the injection of horse serum. In man, Ravdin, Stengel, and Prushankin⁷¹ have observed severe reaction following the infusion of lyophilized serum and have cautioned against its use. Stiuma, Wagner, and Monaghan^{86 87} have abandoned altogether the use of serum and noted freedom from reactions with plasma. Sudden death in man has been noted after the injection of serum¹¹.

What gives rise to this difference between serum and plasma is not known. Biodie⁸ suggests that the active substance is a proteid of the albumin class which is coagulated at 86°F. This active substance is only produced when blood clots, and the interaction of the blood corpuscles is necessary in its formation⁸. Serum obtained from plasma is inactive,⁸ whereas serum separated after clotting may cause severe reactions⁸⁶.

Availability—Type AB plasma, which is free from agglutinins, or such plasma artificially made by mixing Types A and B bloods and removing the plasma,¹⁴ can always be kept on hand for emergency use. The administration of untyped plasma^{16 48 56 87 88} may not be free from danger,* especially in those cases where the titer of the plasma is high and the recipient is markedly anemic⁴⁴.

Storage—Whole blood deteriorates rapidly,⁸⁰ plasma has been preserved for months^{19 31 58}. Decanted plasma carried out by the lyophile process¹⁷ or cryochem-process²⁰ may extend the period of preservation for years. Whether this will hold true for the plasma dried at body temperature, as recently suggested by Edwards, Kay, and Davie,¹⁴ remains to be seen. These methods concentrate the material which may be given in either dilute or concentrated form^{33 34}.

Doses—Filatov and Kaitasevskij¹⁹ use from 150 to 250 cc of plasma as a hemostatic and 300 to 350 cc in shock. Stiuma, *et al*, report 500 cc as the average amount with a range from 250 to 700 cc in the treatment of shock. Mann⁵⁶ recommended a dose of 20 cc per Kg. Recently, 20 Gm of the dried powder in 250 cc of distilled water has been advocated¹⁴.

* Personal communication from Dr. Karl Landsteiner

Electrophoretic protein patterns

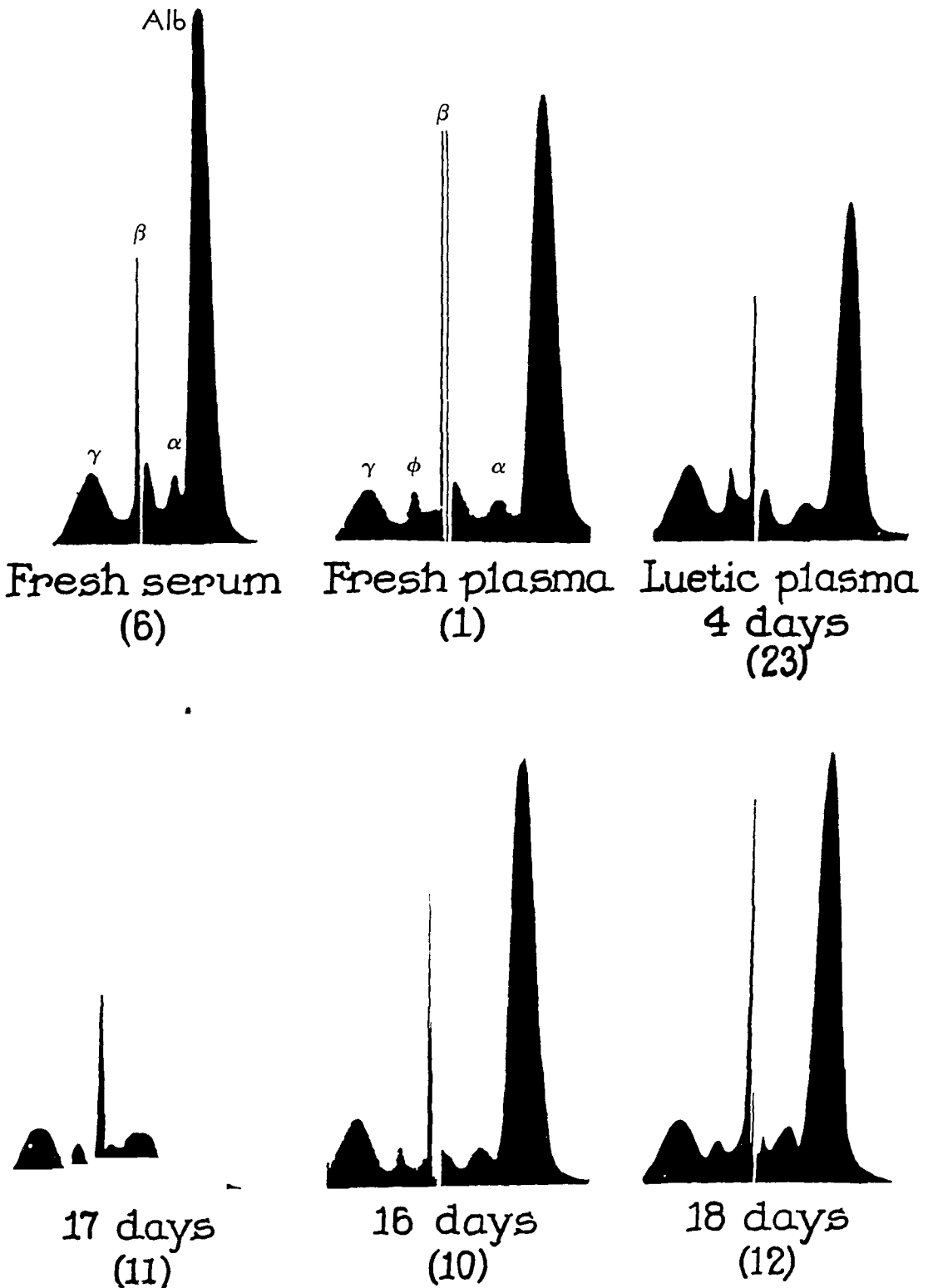
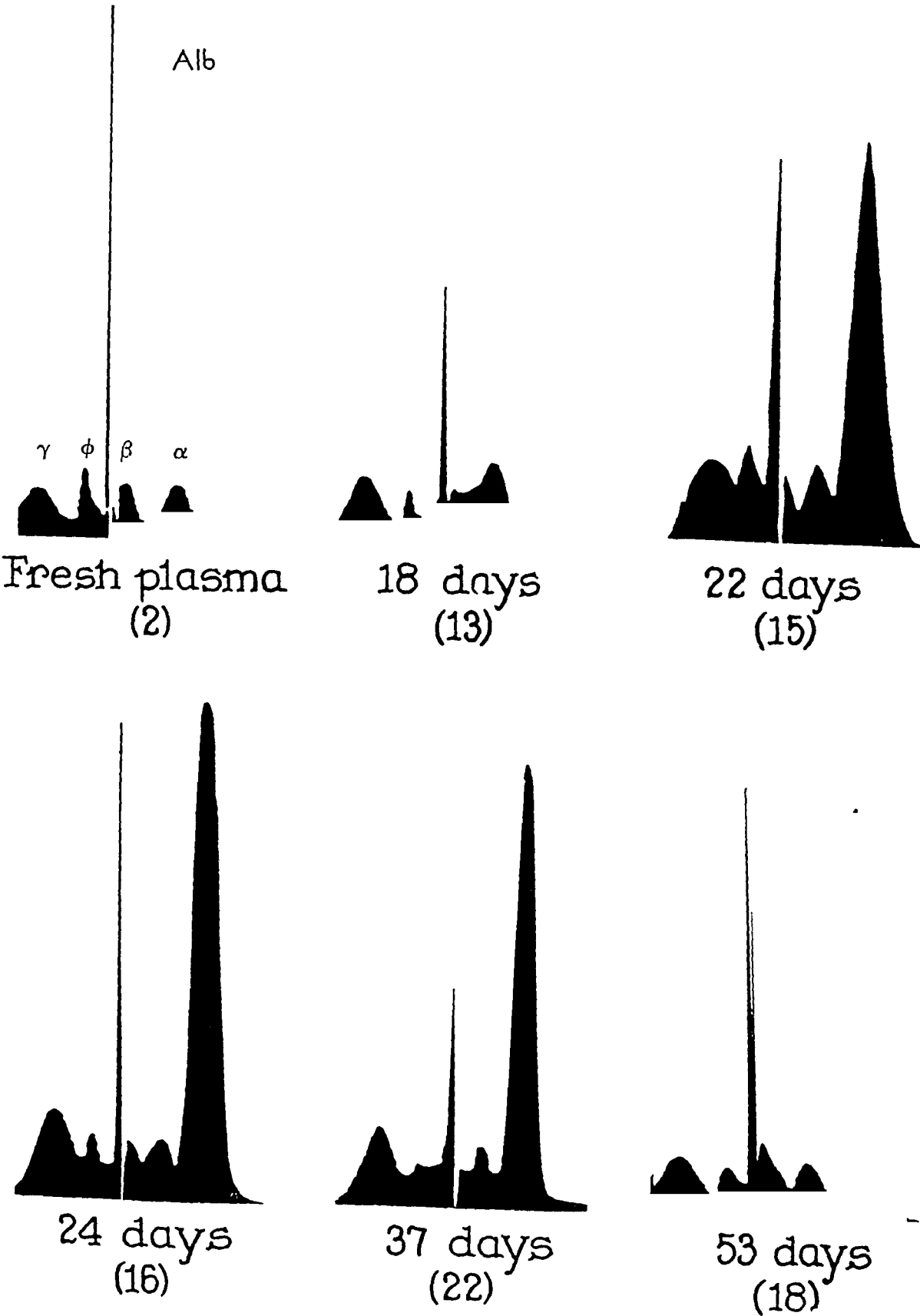


FIG 1

Different refrigerated blood samples



Normal and pathological serum and plasma

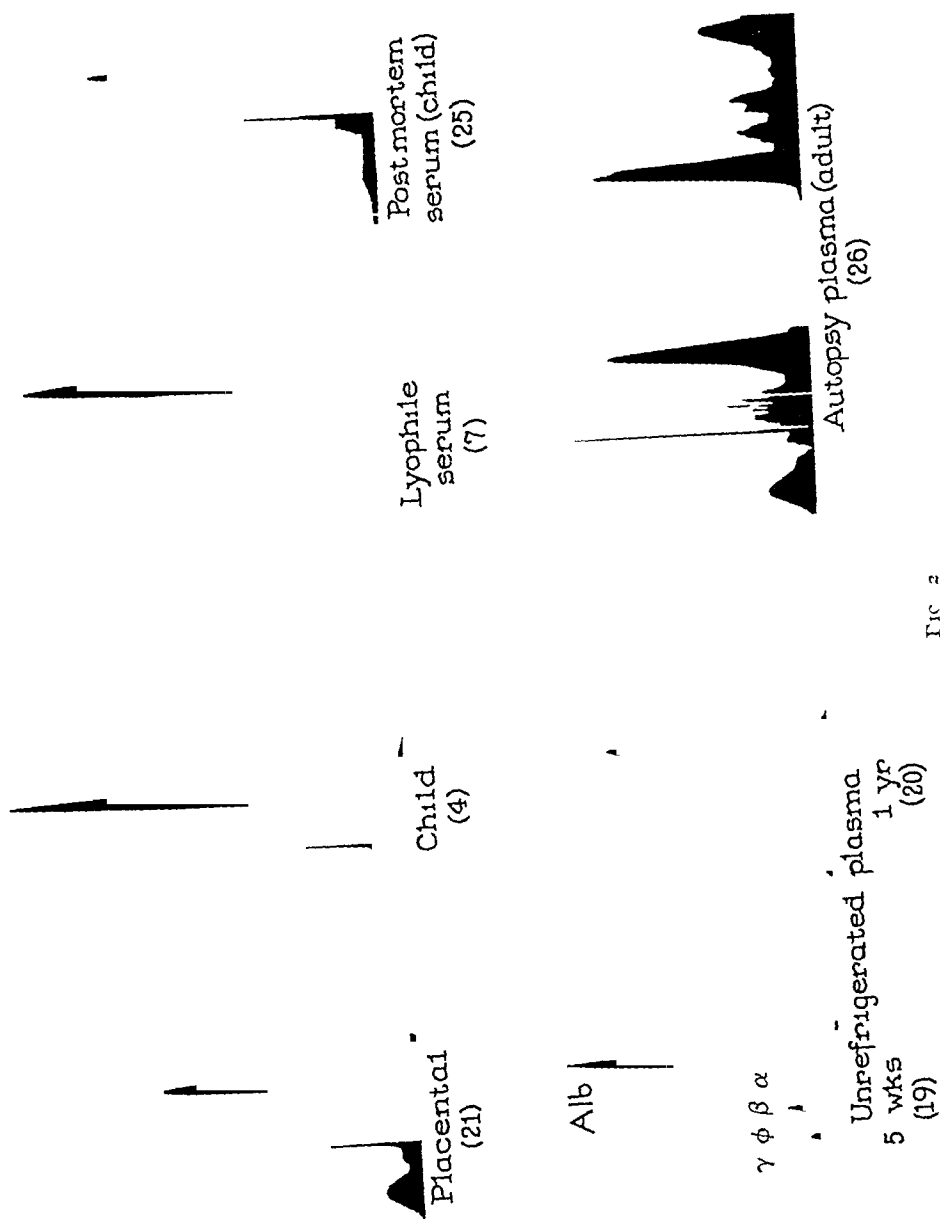


FIG 2

A few of the functions of plasma proteins are outlined in Table I. The various pathologic conditions benefited by plasma are listed in Table II.

The purpose of this investigation is to reexamine these plasma proteins, and to ascertain which factors govern their stability and enhance their preservation.

TABLE I

A FEW FUNCTIONS OF PLASMA PROTEINS

Antibody formation	⁷⁹
Blood pressure increase	⁵⁶
Blood volume maintenance	^{30, 36}
Capillary permeability control	^{12, 13, 11, 82}
Capillary pressure	^{3, 63}
Capillary tone	⁴¹
Clotting	²¹⁻²⁴
Diuresis	^{3, 34}
Edema prevention	^{63, 65, 94, 95}
Hematogenesis	³⁶
Immunity	³⁰
Irritability of cardiac muscle restored	^{7, 26, 28, 12, 15, 57, 70, 72, 76, 85}
Irritability of leached <i>Nitella</i> cells restored	⁶⁹
Kidney function, restored in nephrosis	^{3, 96}
Organ culture	¹⁰
Protection against drugs	¹
Protection against shock	^{33, 97}
Protection against toxins	^{64, 97}
Stabilizing factor	⁹⁷
Tissue culture	¹⁰
Vital	³⁸
Wound repair	²¹

ALBUMIN —Martius⁷⁵ attributed to serum albumin the property of restoring cardiac irritability in the perfused frog's heart. This has been disputed.⁹¹ A less disputed fact is that the smaller albumin molecule is four times as active per gram as the globulin in relation to osmotic pressure.⁶³ Starling⁵⁴ established the endosmotic equivalent of albumin as the factor in maintaining capillary pressure. The importance of albumin in edema formation has again been emphasized.^{63, 94, 95} Following plasmapheresis, the regeneration of albumin is slow⁷¹ after a short early rise.⁸³ This may be accelerated by plasma infusion.⁹⁴ A reversal of the albumin/globulin ratio is seen in certain disease conditions and in preserved blood.⁴⁰

GLOBULIN —By definition, globulins are those proteins which are insoluble in water but soluble in dilute solutions of neutral salts. In plasma, there are four principal globulin components as judged by mobility determinations. *Alpha* globulin is increased in infections,⁵¹ the increase in *beta* globulin may be due to a labile lipoprotein,⁵¹ the *gamma* globulin is associated with an increase in antibodies, while fibrinogen is associated with clotting. von Ott⁷⁰ failed to get good recovery of cardiac irritability with perfusion of globulin through the frog's heart. In contrast to fibrinogen, the reformation of globulin is slow.

after its depletion, though faster than albumin^{37, 38 39, 71} In preserved blood, the increase in the globulin⁴⁰ has been attributed to the protein component from the erythrocyte membrane³⁵

TABLE II

PATHOLOGIC STATES BENEFITED BY SERUM OR PLASMA TRANSFUSIONS

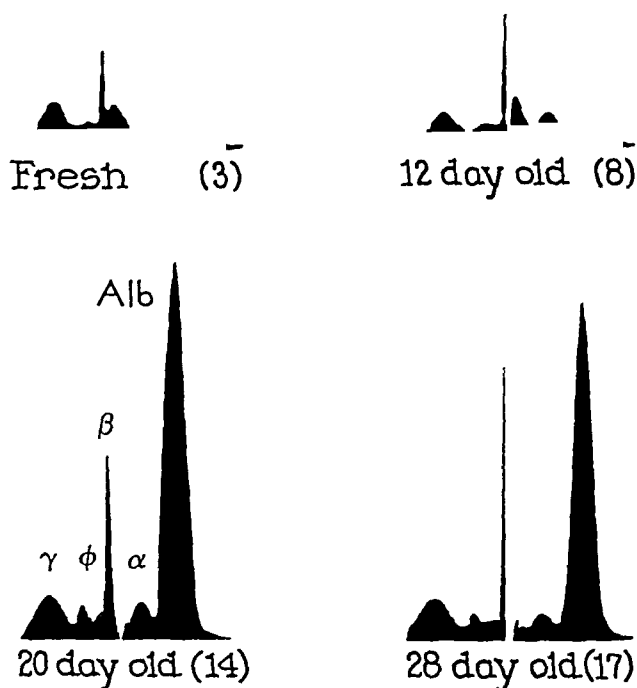
Anemia	^{66 77}
Burns	^{14 15 18 19 29 55 92}
Chickenpox	⁶¹
Cholemia	¹⁹
Edema	^{3 94 95}
Hemorrhage	^{6 9 16 18 74 77 87}
Bleeding gastric ulcer	^{19 29}
Hemorrhagic conditions	^{18 48}
Hemorrhagic disease of new born	⁹⁶
Postoperative hemorrhage	⁸⁷
Pregnancy	¹⁹
Hypoproteinemic states	^{73 82 89 95}
Increased intracranial pressure	³³
Infections, acute hemolytic streptococcus	⁶¹
Intestinal obstruction and strangulation	⁸⁷
Lipoid nephrosis	³
Marasmus	⁹⁶
Mumps	⁶¹
Nephrosis	³⁴
Nutritional edema	^{94 95}
Peritonitis	³
Prematurity	⁹⁶
Scalds	¹⁴
Scarlet fever	⁶¹
Septicemia	⁶⁶
Shock	^{6 16 18 44 47 48 55 56 88 93}
Anesthesia	⁶³
Cold	²⁹
Hemolysis	³¹
Operation	^{14 15 19 63}
Toxins	⁶⁶
Trauma	^{29 87}
Wound	¹⁴
Whooping cough	⁶¹
Wound repair	⁸⁹

FIBRINOGEN—Of the globulins, this appears to be the most homogenous. Its formation is confined to the liver. Foster and Whipple^{21 22 23, 24} have demonstrated that tissue injury is the most powerful stimulus to its formation and that, following depletion, its regeneration is complete in 24 hours. This is in contrast to the other globulins. Liver injury definitely delays this regeneration. Diet, especially cooked pig stomach, accelerates its production.²² With its depletion, celiotomy wounds heal very slowly.²²

Electrophoretic Method of Analysis—Analysis of the various protein components in plasma have been unsatisfactory because of coprecipitation of

the albumin and globulin fractions That albumin-globulin separation by the usual "salting out" methods is by no means sharp has been determined by means of the ultracentrifuge^{59 60} Tiselius demonstrated that the chemical uniformity of a protein could be established through electrophoretic measure-

Electrophoretic patterns of preserved plasma from same donor



Four blood samples taken at different times, collected in 25 per cent sodium citrate and stored in four tubes in electric refrigerator at 4°C Type A blood

FIG 3

ments Both Longworth⁵⁰ and Luetscher,⁵³ using these measurements of Tiselius,⁹⁰ have reaffirmed the inaccuracy of the "salting out" process With the availability of this exact method, the nature and stability of the proteins in preserved blood can now be determined

Procedure—Refrigerated plasma samples of varying ages were obtained

TABLE III
NORMAL PLASMA AND SERUM

No	Material	Composition						Mobilities, $U \times 10^{-3}$						Remarks
		A Per Cent	A/G†	α/A	β/A	γ/A	ϕ/A	p_H	A	α	β	γ	ϕ	
1*	Fresh plasma Type B (J S)	4 68	2 00	0 08	0 24	0 08	0 17	7 62	6 54	5 0	3 5	2 0	0 4	1/5 dilution
2	Fresh plasma Type A†	4 35	2 36	0 12	0 15	0 09	0 16	7 78	5 75	4 3	2 6	1 6	0 2	Citrate
3	Fresh plasma Type A (C R D)	3 96	2 27	0 08	0 18	0 08	0 18	7 72	5 95	4 2	2 9	1 6	0 2	Citrate
4	Fresh plasma Type A (child)	4 11	2 56	0 11	0 14	—	0 14	7 57	5 88	4 5	3 0	—	0 3§	Heparin Oxalate
6	Fresh serum Type B (J S)†	4 76	2 11	0 09	0 21	—	0 18	7 80	5 98	4 3	2 5	—	0 3	
7	Lyophilized serum Type O	5 08	2 17	0 12	0 18	—	0 16	—	6 15	4 5	3 0	—	0 3§	
Mean		4 49	2 25	0 10	0 18	0 08	0 17							

* Refers to figure number in illustration

† A/G calculated on serum basis

‡ Previously reported

§ Mobility figured from *gamma* globulin

from three different Blood Banks in New York City. In addition, unrefrigerated samples were sent for examination from Salisbury, North Carolina. Plasma was obtained also from the autopsy room of the Presbyterian Hospital and placental plasma from the Sloane Hospital for Women, New York City. The reason for selecting the latter two types of plasma is that such blood has been used for transfusions. To ascertain what effect the lyophile process has on serum proteins, a sample of dried serum was supplied by Dr. I. S. Ravdin from Philadelphia.

Method—The electrophoretic method of analysis of proteins has been reported in detail by Longworth and MacInnes^{49, 50, 51}. In brief, a four times diluted portion of plasma is dialyzed in a bag made from cellophane tubing constructed in such a manner as to give a large surface to volume relationship. The buffer with a pH at 7.8 to 25° C consisting of 0.025 M lithium diethyl barbiturate, 0.025 M diethyl barbituric acid, and 0.025 M lithium chloride is used. The dialysis is carried out from 48 to 72 hours in a two liter flask containing fresh buffer at a temperature between 0° and 2° C in a thermostatically controlled electric refrigerator. During the dialysis some precipitate separates out. It is, therefore, necessary to clear the protein solution in an angle centrifuge operated at 0° C before its introduction into the electrophoresis cell. The pH measurement is determined with the glass electrode of MacInnes and Longworth. The conductivity cell is of special design⁵¹ as well as the screened bridge used for the measurement of electrolytic conductance⁸¹. The establishment of a Donnan equilibrium is assumed when further dialysis produces no change in conductance of the protein solution and the outside solution has the conductance of the original buffer. The manner of obtaining the protein patterns and of computing the different mobilities of the protein constituents has been published by Longworth, Shedlovsky, and MacInnes⁵¹.

TABLE IV

	Longworth	Luetscher	This Series	Preserved
Albumin per cent	4.38	4.06	4.49	3.73
Albumin/globulin*	1.85	2.00	2.25	1.74
<i>Alpha</i> globulin albumin	0.12	0.11	0.10	0.12
<i>Beta</i> globulin albumin	0.23	0.21	0.18	0.23
<i>Gamma</i> globulin albumin	0.21	0.18	0.17	0.24
Fibrinogen albumin	0.09	0.09	0.08	0.09
Number of analyses	7	?	6	12

* Estimated on serum basis

Results—The normal values (Table III) compare with those reported by Longworth, Shedlovsky, and MacInnes, and Luetscher (Table IV, columns 1, 2, 3). In column 4, the mean values for plasma preserved 12 to 53 days are tabulated.

Discussion—In comparing the values for preserved plasma with the values for fresh plasma reported in this series and in others, several points

TABLE V
PRESERVED NORMAL PLASMA

No	Material	Age of Blood Days	Composition					Mobilities, $U \times 10^{-5}$					Remarks		
			A Per Cent	A/G†	α/A	β/A	γ/A	ϕ/A	p_H	A	α	β		γ	ϕ
			REFRIGERATED												
8*	C R D (same as 3)	12	3 81	1 92	0 11	0 21	0 07	0 20	7 71	6 15	4 3	2 9	1 6	0 1	Citrate
9	Bellevue No 1827 Type O	12	3 76	1 33	0 17	0 28	0 17	0 30	7 81	5 83	4 1	2 8	1 7	0 3	Citrate
10	J S (same as 1, 6)	16	3 18	1 67	0 11	0 23	0 08	0 26	7 58	—	—	—	—	—	Citrate
11	Mt Sinai No 2845	17	4 22	2 10	0 14	0 17	0 06	0 16	7 83	6 07	4 2	2 9	1 8	0 3§	Citrate (ri- day cells) Citrate
12	Bellevue No 1776 Type A	18	3 67	1 67	0 11	0 27	0 09	0 22	7 81	5 82	4 3	2 9	1 7	0 2	Citrate
13	H H Type A Special bottle	18	4 08	2 04	0 14	0 17	0 06	0 18	7 57	6 18	4 5	2 8	1 7	0 1	Citrate (col- lected in CO ₂) Citrate
14	C R D (same as 3, 8)	20	3 66	1 72	0 11	0 21	0 09	0 26	7 73	6 25	4 6	3 2	1 7	0 2	Citrate
15	Bellevue No 1737 Type AB	22	3 58	1 67	0 14	0 21	0 13	0 25	7 78	5 72	4 1	2 9	1 6	0 3	Citrate
16	Mt Sinai No 2821 Type A	24	4 13	1 75	0 12	0 21	0 08	0 24	7 83	6 06	4 3	3 2	1 7	0 2	Citrate
17	C R D (Same as 3, 8, 14)	28	2 89	1 54	0 12	0 27	0 08	0 26	7 75	6 18	4 5	3 1	1 7	0 3§	Citrate
22	Bellevue Ultracentrifuge	35	3 72	1 70	0 10	0 22	0 09	0 27	7 67	6 00	4 4	3 2	1 7	0 1	Citrate
18	Mt Sinai† Special flask	53	4 09	1 72	0 11	0 25	0 09	0 22	—	5 70	4 0	2 5	1 6	0 1	Citrate
Mean			3 73	1 74	0 12	0 23	0 09	0 24							

* Refers to figure number in illustration

† A/G figured on serum basis

‡ Previously reported

§ Mobility figured from gamma globulin

TABLE VI
PRESERVED PLASMA NORMAL AND ABNORMAL

No	Material	Age of Blood Days	Composition						Mobilities, $U \times 10^{-3}$					Remarks		
			A Per Cent	A/G†	α/A	β/A	γ/A	ϕ/A	p_H	A	α	β	γ		ϕ	
UNREFRIGERATED																
19*	Saline diluted plasma	35	2 64	1 90	0 21	0 12	0 09	0 20	7 82	6 40	5 10	3 5	2 0	0 6	From North Carolina	
20	Saline diluted plasma	356	3 33	1 82	0 22	0 13	0 07	0 20	7 80	6 45	4 80	3 3	2 1	0 5	From North Carolina	
21	Placental plasma	0	3 47	2 00	0 13	0 16	0 05	0 21	7 85	6 30	4 80	3 0	1 9	0 1	Oxalate	
23	Luetic plasma	4	2 50	1 54	0 12	0 21	0 18	0 32	7 85	6 17	4 60	3 1	1 7	0 1	Citrate	
25	Autopsy serum (child)	—	4 22	1 92	0 13	0 25	—	0 14	—	—	—	—	—	—		
26	Autopsy plasma	—	3 28	0 96	0 26	0 42	0 07	0 36	—	—	—	—	—	—		

* Refers to figure number in illustration
† A/G figured on serum basis

may be made. The greatest change appears in the decrease of albumin as well as a change in the components which constitute the albumin/globulin ratio. Fibrinogen appears unaltered. A definite increase appears in the *gamma* globulin. This decrease in albumin and increase in *gamma* globulin have been previously noted by Knoll⁴⁰. It is of interest that the two specimens which had been kept in a specially designed bottle⁵⁰ showed the least changes.

In comparing the refrigerated samples with those that had been kept at room temperature and had been shipped about the country, the greatest difference is seen in the *beta* globulin fraction. In the diagram, the *beta* globulin disturbance (indicated by the thin spike in the *beta* globulin region) is absent and the *beta* globulin/albumin ratio is decreased.

Both the autopsy serum from the child and the plasma from the adult were abnormal. The placental plasma appeared within normal limits. The lyophilized serum presented an anomaly in that the *beta* disturbance was missing.

No conclusions can be drawn from this small series, certain indications, however, may be followed out. First as to the source of the preserved blood. Postmortem blood appears abnormal, this may not apply to blood collected from those who have met sudden death. Placental blood would appear to be a normal source for conserved blood. Lyophilized serum appears abnormal. Refrigeration seems to enhance the preservation of plasma as did the shape of the flask. Possibly denaturation^{99, 100} of plasma proteins is slower under these conditions.

SUMMARY

(1) The relationship of plasma to vitality of both vegetable and animal cells is reviewed.

(2) Plasma approaches the ideal physiologic perfusion fluid, and is superior to acacia, glucose salt, and serum.

(3) Electrophoretic patterns of six normal, 14 preserved, and four miscellaneous plasmas are presented.

(4) Refrigerated plasma appears to be stable and shows only minor changes up to 53 days' storage. The A/G ratio declines, due principally to a decrease in the albumin component.

(5) Unrefrigerated plasma, lyophilized serum, and autopsy plasma appear definitely abnormal.

Appreciation is herewith expressed to Dr. D. A. MacInnes for both his help and encouragement in the conduction of these studies and to Drs. L. G. Longworth and T. Shedlovsky for their aid and cooperation as well as for permission to use some of their material. To the authorities in charge of the Blood Banks at the Mt. Sinai, Bellevue, and Presbyterian Hospitals in New York, a debt of gratitude is expressed for the supply of the various plasmas tested. For the donation of the unrefrigerated plasma specimens which were shipped to us from Salisbury, North Carolina, by Dr. J. Elliott, acknowledgment is here made. The lyophilized serum was supplied to us through the kindness of Dr. I. S. Ravdin, of Philadelphia. The opportunity to conduct these studies

was made possible through a Fellowship from the Commonwealth Fund, New York. In part, the expenses of this investigation were defrayed through a grant from the Blood Transfusion Betterment Association, New York.

In conclusion, this program of work, its direction and fulfillment are a part of the investigative work sponsored by Dr. Allen O. Whipple, of the College of Physicians and Surgeons, Columbia University, New York.

BIBLIOGRAPHY

- ¹ Abel, J. J., Rowntree, L. G., and Turner, B. B. Plasma Removal with Return of Corpuscles (Plasmapheresis). *Jour Pharm and Exper Therap*, 5, 625-641, 1913-1914.
- ² Achard, C., Levy, J., and Gallais, F. Recherches experimentales sur quelques modifications colloïdales produites dans le serum sanguin par l'injection de serum concentre et par les saignees plasmatiques. *Compt Rend Acad d sc*, 194, 1773-1777, 1932.
- ³ Aldrich, C. A., Stokes, J., Jr., Killingsworth, W. P., and McGinness, A. C. Concentrated Human Blood Serum as a Diuretic in the Treatment of Nephrosis. *J A M A*, 111, 129-133, 1938.
- ⁴ Amberson, W. R. Blood Substitutes. *Biol Rev*, 12, 48-86, 1937.
- ⁵ Belt, A. E., Smith, H. P., and Whipple, G. H. III. Factors Concerned in the Perfusion of Living Organs and Tissues. Artificial Solutions Substituted for Blood Serum and the Resulting Injury to Parenchyma Cells. *Am Jour Physiol*, 52, 101-120, 1920.
- ⁶ Bond, D. D., and Wright, D. G. Treatment of Hemorrhage and Traumatic Shock by the Intravenous Use of Lymphophilic Serum. *ANNALS OF SURGERY*, 107, 500-510, 1938.
- ⁷ Bowditch, H. P. Über die Eigenthümlichkeiten der Reizbarkeit, welche die Muskelfasern des Herzens zeigen. *Arbeit a d physiol Anstalt z Leipzig*, 6, 139-176, 1871.
- ⁸ Brodie, T. G. The Immediate Action of an Intravenous Injection of Blood-Serum. *Jour Physiol*, 26, 48-71, 1900.
- ⁹ Brodin, P., and Saint-Girons, F. La transfusion sanguine en utilisant le plasma au lieu du sang total dans les grandes hemorragies. *Bull et mem Soc Med d Hôp d Paris*, 55, 1224-1226, 1939.
- ¹⁰ Carrel, A., and Lindbergh, C. A. The Culture of Whole Organs. *Science*, n s, 81, 621-623, 1935.
- ¹¹ Current Comment. Sudden Death after Injection of Human Serum. *J A M A*, 103, 192, 1934.
- ¹² Drinker, C. K. The Permeability and Diameter of the Capillaries in the Web of the Brown Frog (*R. Temporaria*) When Perfused with Solutions Containing Pituitary Extract and Horse Serum. *Jour Physiol*, 63, 249-269, 1927.
- ¹³ Drinker, C. K., and Field, M. E. *Lymphatics, Lymph and Tissue Fluid*. Baltimore, Williams and Wilkins, 1933.
- ¹⁴ Edwards, F. R., Kay, J., and Davie, T. B. * The Preparation and Use of Dried Plasma for Transfusion. *Brit Med Jour*, 1, 377-381, 1940.
- ¹⁵ Elkinton, J. R., Gilmour, M. T., and Wolff, W. A. The Control of Water and Electrolyte Balance in Surgical Patients. *ANNALS OF SURGERY*, 110, 1050-1066, 1939.
- ¹⁶ Elliott, J. A Preliminary Report of a New Method of Blood Transfusion. *South Med and Surg*, 98, 643-645, 1939.
- ¹⁷ Elser, W. J., Thomas, R. A., and Steffen, G. I. The Desiccation of Sera and Other Biological Products (Including Micro-organisms) in the Frozen State with the Preservation of the Original Qualities of Products So Treated. *Jour Immunol*, 28, 433-473, 1935.

* See illustration on page 519

- ¹⁸ Fantus, B The Therapy of the Cook County Hospital Blood Preservation J A M A , 109, 128-131, 1937
- ¹⁹ Filatov, A, and Kartasevskij, N Die Transfusion von menschlichem Blutplasma als blutstillendes Mittel Zentralbl f Chir , 62,¹ 441-445, 1935
- ²⁰ Flosdorf, E W, and Mudd, S An Improved Procedure and Apparatus for Preservation of Sera, Micro-organisms and Other Substances—The Cryochem-Process Jour Immunol , 34, 469-490, 1938
- ²¹ Foster, D P, and Whipple, G H Blood Fibrin Studies I An Accurate Method for the Quantitative Analysis of Blood Fibrin in Small Amounts of Blood Am Jour Physiol , 58, 365-378, 1921-1922
- ²² Foster, D P, and Whipple, G H Blood Fibrin Studies II Normal Fibrin Values and the Influence of Diet Am Jour Physiol , 58, 379-392, 1921-1922
- ²³ Foster, D P, and Whipple, G H Blood Fibrin Studies III Fibrin Values Influenced by Transfusion, Hemorrhage, Plasma Depletion, and Blood Pressure Changes Am Jour Physiol , 58, 393-406, 1921-1922
- ²⁴ Foster, D P, and Whipple, G H Blood Fibrin Studies IV Fibrin Values Influenced by Cell Injury, Inflammation, Intoxication, Liver Injury and the Eck Fistula Am Jour Physiol , 58, 407-431, 1921-1922
- ²⁵ Freeman, N E, and Wallace, W McL The Effect of Concentrated Serum on Plasma Volume and Serum Protein Concentration Am Jour Physiol , 124, 791-799, 1938
- ²⁶ Gaule, J Die Leistungen des entbluteten Froschherzens Arch f Anat u Physiol Lpz Physiol Abt , 291-311, 1878
- ²⁷ Gorham, L W, and Morrison, A W The Action of the Proteins of Blood upon the Isolated Mammalian Heart Am Jour Physiol , 25, 419-432, 1910
- ²⁸ Guthrie, C C, and Pike, F H The Relation of the Activity of the Excised Mammalian Heart to Pressure in the Coronary Vessels and to Its Nutrition Am Jour Physiol , 18, 14-38, 1907
- ²⁹ Harkins, Henry N Surgical Shock from Burns, Freezing, and Similar Traumatic Agents Colorado Med , 33, 871-876, 1936
- ³⁰ Heidelberger, M Relation of Proteins to Immunity, Schmidt, C L A Chemistry of the Amino Acids and Proteins Springfield, Illinois Charles C Thomas, 953-974, 1938
- ³¹ Heimatz, S W, and Sokolow, N I Plasmatransfusion als Methode der Wahl in der Behandlung des hamolytischen Schocks Zentralbl f Chir , 62, 1753-1755, 1935
- ³² Howell, W H, and Cooke, E Action of the Inorganic Salts of Serum, Milk, Gastric Juice, etc , upon the Isolated Working Heart, with Remarks upon the Causation of the Heart-beat Jour Physiol , 14, 198-220, 1893
- ³³ Hughes, J, Mudd, S, and Strecker, E A Treatment of Increased Intracranial Pressure by Concentrated Human Lyophile Serum Tr Am Neurol Assn , 118-123, 1936
- ³⁴ Jeans, P C The Use of Lyophile Serum Jour Iowa State Med Soc , 29, 64-66, 1939
- ³⁵ Jorpes, E The Protein Component of the Erythrocyte Membrane or Stroma Biochem Jour , 26,² 1488-1503, 1932
- ³⁶ Kallius, H U Experimentelle Untersuchungen uber die Wirkung des Serums bei der vitalen Bluttransfusion Deutsch Ztschr f Chir , 212, 289-307, 1928
Idem Die Verweildauer der gebrauchlichen Blutersatzflussigkeiten, insbesondere transfundierten Serums, nach grossen Blutverlusten im Tierversiment Deutsch Ztschr f Chir , 220, 216-238, 1929
- ³⁷ Kerr, W J, Hurwitz, S H, and Whipple, G H Regeneration of Blood Serum Proteins I Influence of Fasting upon Curve of Protein Regeneration Following Plasma Depletion Am Jour Physiol , 47, 356-369, 1918-1919

- ³⁸ Kerr, W J, Hurwitz, S H, and Whipple, G H Regeneration of Blood Serum Protein II Influence of Diet upon Cuive of Protein Regeneration Following Plasma Depletion *Am Jour Physiol*, 47, 370-378, 1918-1919
- ⁹ Kerr, W J, Hurwitz, S H, and Whipple, G H Regeneration of Blood Serum Proteins III Liver Injury Alone Liver Injury and Plasma Depletion The Eck Fistula Combined with Plasma Depletion *Am Jour Physiol*, 47, 379-392, 1918-1919
- ⁴⁰ Knoll, H Experimenteller Beitrag zur Frage der Bluttransfusion mit konserviertem Blut *Deutsch Ztschr f Chir*, 252, 463-477, 1939
- ⁴¹ Krogh, A, and Harrop, G A On the Substance Responsible for Capillary Tonus *Jour Physiol, Proc Physiol Soc*, 54, 125, 1921
- ⁴² Kronecker, H, and Stirling, W Das charakteristische Merkmal der Herzmuskelbewegung *Beitr z Anat Physiol als Festgabe Carl Ludwig, gewidmet von seinen Schuelern, Leipzig, F C W Vogel*, 173-204, 1874
- ⁴³ Kunz, H Zur Frage der Transfusion artfremden Blutes *Deutsch Ztschr f Chir*, 220, 196-215, 1929
- ⁴⁴ Kunz, H Über die Infusion artgleichen Serums *Zentralbl f Chir*, 59,¹ 1003-1006, 1932
- ⁴⁵ Langendorff, O Untersuchungen am überlebenden Saugethierherzen *Arch f d ges Physiol*, 61, 291-332, 1895
- ⁴⁶ Le Gallois, C J J Experiences sur le principe de la vie *Paris, D Hautel*, 1812
- ⁴⁷ Lehman, E P A Simple Method of Plasma Transfusion *J A M A*, 112, 1406-1407, 1939
- ⁴⁸ Levinson, S O, Neuwelt, F, and Necheles, H Human Serum as a Blood Substitute in the Treatment of Hemorrhage and Shock *J A M A*, 114, 455-461, 1940
- ⁴⁹ Longworth, L G A Modification of the Schlieren Method for Use in Electrophoretic Analysis *Jour Am Chem Soc*, 61, 529-530, 1939
- ⁵⁰ Longworth, L G, and MacInnes, D A Electrophoresis of Proteins by the Tiselius Method *Chem Reviews*, 24, 271-287, 1939
- ⁵¹ Longworth, L G, Shedlovsky, T, and MacInnes, D A Electrophoretic Patterns of Normal and Pathological Human Blood Serum and Plasma *Jour Exper Med*, 70, 399-413, 1939
- ⁵² Luciani, L Eine periodische Function des isolirten Froschherzens *Arbeit a d physiol Anstat zu Leipzig*, 7, 114-196, 1872
- ⁵³ Luetscher, J A, Jr Electrophoretic Analysis of Plasma and Urinary Proteins *Jour Clin Invest*, 19, 313-320, 1940
- ⁵⁴ MacInnes, D A, and Longworth, L G The Measurement and Regulation of pH with the Glass Electrode *Trans Electro-Chem Soc*, 71, 73-91, 1937
- ⁵⁵ Mahoney, E B A Study of Experimental and Clinical Shock with Special Reference to Its Treatment by the Intravenous Injection of Preserved Plasma *ANNALS OF SURGERY*, 108, 178-193, 1938
- ⁵⁶ Mann, F C Further Experimental Study of Surgical Shock *J A M A*, 71, 1184-1188, 1918
- ⁵⁷ Martius, F Die Erschopfung und Ernährung des Froschherzens *Arch f Anat u Physiol Lpz Physiol Abt*, 543-562, 1882
- ⁵⁸ McClure, R D The Treatment of the Patient with Severe Burns *J A M A*, 113, 1808-1812, 1939
- ⁵⁹ McFarlane, A S The Behavior of Pathological Sera in the Ultracentrifuge *Biochem Jour*, 29,¹ 1175-1201, 1935
- ⁶⁰ McFarlane, A S The Ultracentrifugal Analysis of Normal and Pathological Serum Fractions *Biochem Jour*, 29,¹ 1209-1226, 1935
- ⁶¹ McGuiness, A C, Stokes, J, Jr, and Mudd, S The Clinical Uses of Human Serums Preserved by the Lyophile Process *Jour Clin Invest*, 16, 185-196, 1937

- ⁶² Merunowicz Über die chemischen Bedingungen für die Entstehung des Herzschlages Arb a d physiol Anstalt zu Leipzig, 10, 132-178, 1875
- ⁶³ Moore, N S, and Van Slyke, D D The Relationships between Plasma Specific Gravity, Plasma Protein Content and Edema in Nephritis Jour Clin Invest, 8, 337-355, 1930
- ⁶⁴ Morawitz, P Beobachtungen über den Wiederersatz der Bluterweisskörper Beitr z chem Phys u Path, 7, 153-164, 1906
- ⁶⁵ Muntwyler, E, Way, C T, Binns, D, and Myers, V C Plasma Protein and Plasma Colloid Osmotic Pressure in Pathological Conditions with Special Reference to the Occurrence of Edema Jour Clin Invest, 12, 495-504, 1933
- ⁶⁶ Nicholson, P Notes on the Treatment of an Unusual Case of Hemolytic Streptococcus Septicemia Jour Pediat, 8, 363-366, 1936
- ⁶⁷ Oehlecker, F Ist die Bluttransfusion völlig ungefährlich, wenn Vorher eine Blutgruppenbestimmung gemacht worden ist? Med Klin, 37, 1421-1424, 1928
- ⁶⁸ Oehlecker, F Indikation zur Bluttransfusion Der Chirurg, 1, 577-584, 1929
- ⁶⁹ Osterhout, W J V Chemical Restoration in Nitella II Restorative Action of Blood Jour General Physiol, 19, 423-425, 1936
- ⁷⁰ von Ott Über die Bildung von Leistungs Serumalbumin im Magen und über die Fähigkeit der Milch das Froschherz leistungs-fähig zu halten Arch f Anat u Physiol Lpz Physiol Abt, 1-26, 1883
- ⁷¹ Peters, John P, and Van Slyke, Donald D Quantitative Clinical Chemistry Interpretations, Baltimore, Williams and Wilkins, 1, 1931
- ⁷² Popoff, N Über die Bildung von Serumalbumin im Darmkanale Ztschr F Biol, 25, 427-452, 1889
- ⁷³ Ravdin, I S, Stengel, A, Jr, Prushankin, M The Control of Hypoproteinemia in Surgical Patients J A M A 114, 107-112, 1940
- ⁷⁴ Richet, C, Brodin, P, and Saint-Girons, F Des injections de plasma sanguin pour remplacer le sang total Presse med 26,² No 62, 579-580, 1918
- ⁷⁵ Ringer, S Concerning the Influence Exerted by Each of the Constituents of the Blood on the Contraction of the Ventricle Jour Physiol, 3, 380-393, 1880-1882
- ⁷⁶ Ringer, S Regarding the Influence of the Organic Constituents of the Blood on the Contractility of the Ventricle Jour Physiol, 6, 361-381, 1885
- ⁷⁷ Rossius, L Ein tiereperimenteller Beitrag zur Frage der Bluttransfusion Arch f klin Chr, 137, 583-618, 1925
- ⁷⁸ Rous, P, and Wilson, G W Fluid Substitutes for Transfusion after Hemorrhage J A M A, 70, 219-222, 1918
- ⁷⁹ Schmidt, Carl L A The Chemistry of the Amino Acids and Proteins Springfield, Ill, Charles C Thomas, 1938
- ⁸⁰ Scuddei, John Shock Blood Studies as a Guide to Therapy Philadelphia, J B Lippincott Company, 1940
- ⁸¹ Shedlovsky, T A Screened Bridge for the Measurement of Electrolytic Conductance I Theory of Capacity Errors, II Description of the Bridge Jour Am Chem Soc, 52, 1793-1805, 1930
- ⁸² Smith F, and Dick, M The Influence of the Plasma Colloids on the Gradient of Capillary Permeability Jour Exper Med, 56, 371-389, 1932
- ⁸³ Smith, H P, Belt, A E, and Whipple, G W I Rapid Blood Plasma Protein Depletion and the Curve of Regeneration Am Jour Physiol, 52, 54-71, 1920
- ⁸⁴ Starling, E H On the Absorption of Fluids from the Connective Tissue Spaces Jour Physiol, 19, 312-326, 1895-1896
- ⁸⁵ Stenon Die Beteiligung der einzelnen Stoffe des Serums an der Erzeugung des Herzschlages Arch f Anat u Physiol Lpz Physiol Abt, 263-290, 1878
- ⁸⁶ Struma, M M, Wagner, J A, and Monaghan, J F The Intravenous Use of Serum and Plasma, Fresh and Preserved ANNALS OF SURGERY, 111, 623-629, 1940

- ⁸⁷ Strumia, M M, Wagner, J A, and Monaghan, J F The Use of Citrated Plasma in the Treatment of Secondary Shock J A M A, 114, 1337-1341, 1940
- ⁸⁸ Tatum, W L, Elliott J, and Nessel, N A Technique for the Preparation of a Substitute for Whole Blood Adaptable for Use During War Conditions Mil Surgeon, 85, 481-489, 1939
- ⁸⁹ Thompson, W D, Ravdin, I S, Rhoads, J E, and Frank, I L Use of Lyophile Plasma in Correction of Hypoproteinemia and Prevention of Wound Disruption Arch Surg, 36, 509-518, 1938
- ⁹⁰ Tiselius, A The Moving Boundary Method of Studying the Electrophoresis of Proteins Uppsala, Almqvist and Wiksells Boktryckeri-A-B, 1930
- ⁹¹ Walden, E C Comparison of the Effect of Certain Inorganic Solutions and Solutions Containing Serum Albumin on the Rhythmic Contractility of the Frog's Heart Am Jour Physiol, 3, 123-133 1899
- ⁹² Walther, W W Blood Changes after Surgical Operations Lancet, 1, 6-9, 1937
- ⁹³ Ward, G R Transfusion of Plasma Brit Med Jour, 1, 301, 1918
- ⁹⁴ Weech, A A, Goettsch, E, and Reeves, E B The Effect of Serum Transfusion on the Plasma Protein Depletion Associated with Nutritional Edema in Dogs Jour Clin Invest, 12, 217-227, 1933
- ⁹⁵ Weech, A A, Snelling, C E, and Goettsch, E The Relation Between Plasma Protein Content, Plasma Specific Gravity and Edema in Dogs Maintained on a Protein Inadequate Diet and in Dogs Rendered Edematous by Plasmapheresis Jour Clin Invest, 12, 193-216, 1933
- ⁹⁶ Welch, J E Normal Human Blood Serum in the Treatment of Hemorrhagic Diseases of Infants and Children New York Med Jour, 97, 125-128, 1913
- ⁹⁷ Whipple, G H, Smith, H P, and Belt, A E II Shock as a Manifestation of Tissue Injury Following Rapid Plasma Protein Depletion The Stabilizing Value of Plasma Proteins Am Jour Physiol, 52, 72-100, 1920
- ⁹⁸ Wieland, H Entgiftung durch adsorptive Verdrangung Ein Beitrag zur Kenntnis der Ermudung des uberlebenden Froschherzens und der Heizwirkung des Kampfers Arch exp Path Pharmac, 89, 46-65, 1921
- ⁹⁹ Wu, H Studies on Denaturation of Proteins II Coagulation by Alcohol Chinese Jour Physiol, 1, 81-88, 1927
- ¹⁰⁰ Wu, H, and Ling, S M Studies on Denaturation of Proteins V Factors Controlling Coagulation of Proteins by Shaking Chinese Jour Physiol, 1, 407-428, 1927

Electrophoretic patterns of same plasma

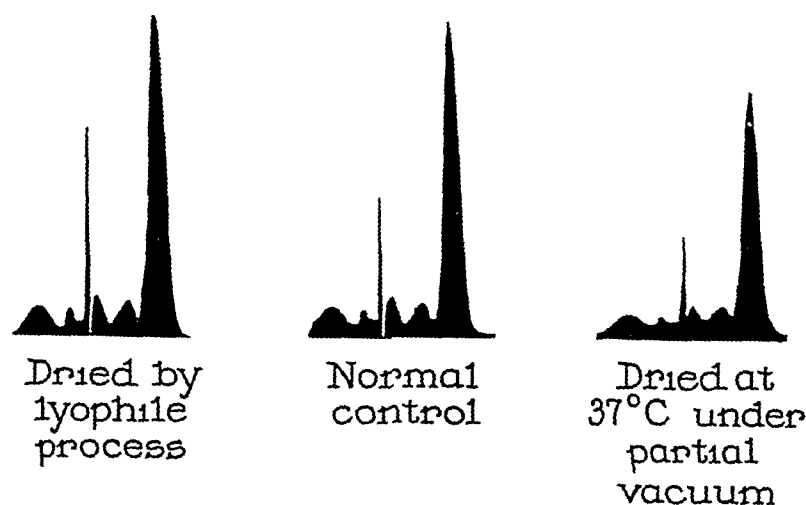


FIG 4—Plasma dried according to method of Edwards Kay and Davie¹⁴ on the right hand side Note the difference between this and the other two

SODIUM CHLORIDE METABOLISM OF SURGICAL PATIENTS*

WALTER G MADDOCK, M D

AND

FREDERICK A COLLER, M D

ANN ARBOR, MICH

FROM THE DEPARTMENT OF SURGERY OF THE UNIVERSITY OF MICHIGAN ANN ARBOR, MICH

THREE CONDITIONS may materially alter the sodium chloride metabolism of the surgical patient from that of the normal (1) A reduction in the intake of salt through inability to take anything by mouth, (2) the frequent occurrence of abnormal losses of fluid containing salt, and (3) a tendency for the retention of salt and water when the patient is seriously ill and the intake of salt has been excessive With these conditions in mind, sodium chloride therapy is best handled with a knowledge of the fundamental processes involved

Normal Sodium Chloride Metabolism—Sodium chloride is the most abundant electrolyte in the blood and interstitial body fluid, while for intracellular fluids, potassium and phosphate are the chief ions^{1 2} Sodium chloride has two vital functions (1) It helps to maintain the acid base balance of the body, and (2) it is largely responsible for the total osmotic pressure of the extracellular fluids Gamble^{2, 3} has aptly pointed out that the electrolytes really sustain the blood and interstitial fluids, and while one's attention is frequently drawn to other substances, such as the blood sugar the amino-acids, the lipids, and the nitrogenous waste products, these are simply the nutrient or waste materials being transported to and from the cells by their real environment of salt solution And further, while the volume of the extracellular vehicle fluid is dependent upon the amount of the electrolytes, Gamble and Ross⁴ have pointed out that sodium ions are more important than chloride ions in this regard, since sodium cannot be replaced by any other anion while chloride loss can be replaced by bicarbonate ions formed from the carbon dioxide of catabolism A preponderant loss of sodium thus leads to greater dehydration than a predominate loss of chlorides

The normal balance of sodium chloride is maintained by a daily intake of from 1 to 2 Gm in the food itself⁵ and from 2 to 8 Gm added in the process of cooking and the vigorous use of the salt shaker at the table To this oral ingestion, from eight to ten liters of salt-containing solution, made up of gastric juice, bile, pancreatic secretion, and succus entericus, are poured into the upper part of the intestinal tract daily Body economy is shown by the fact that 95 per cent or more of the sodium chloride is absorbed lower down in the intestinal tract, and the daily salt loss in the stool

* Aided by a grant from the Horace H Rackham School of Graduate Studies

Read before the American Surgical Association, St Louis, Mo., May 1, 2, 3, 1940

is normally less than 0.5 Gm a day^{5, 6} Important amounts of sodium chloride are normally excreted by the body in two ways One is through the sweat glands and varies with their activity With insensible perspiration insignificant losses of salt occur, Freyberg and Giant⁷ having reported from 0.25 to 0.41 Gm per day Active sweating has produced excretions as high as 2 Gm an hour,⁸ but this is exceptional It has been shown that an adaptation to extreme dry heat takes place, and the salt loss in sweat is much reduced⁹ The kidneys maintain the salt balance by excreting the excess intake, and they usually put out from 3 to 8 Gm of sodium chloride a day This is but one example of the kidneys' important function of maintaining a certain concentration of substances in solution in the body fluids, and excreting the remainder

To provide some salt to patients taking nothing by mouth and, therefore, requiring parenteral fluids, we believe that if no abnormal losses of sodium chloride have occurred, each patient should be given half a liter of Ringer's solution daily, and the remainder of the fluid needs should be supplied by 5 or 10 per cent dextrose in distilled water The 4 to 5 Gm of sodium chloride thus given will provide for daily metabolic needs and adjustments and at the same time will avoid edema from excess salt

The Conservation of Electrolytes by the Body—The observations of many workers^{3, 5, 10, 11, 12} have shown that when no sodium chloride is taken in or when the balance is disturbed by abnormal losses, as in vomitus, the kidneys reduce this excretion to a minimum and conserve salt Our associates, Bartlett, Bingham and Pedersen,¹³ found the fact well demonstrated in their experimental production of hypochloremia in humans Benedict,¹⁴ in 1915, reported the chloride excretion in the urine of a subject who fasted for 31 days, and found that 12.3 Gm of chloride or 20.3 Gm of sodium chloride were put out during that time Half of this amount was excreted in the first four days, during the later days only traces of chloride were found in the urine

In the practical handling of surgical patients it can be assumed without chemical studies that their sodium chloride concentration will be normal if the patient has been eating a good, general diet and has had no abnormal losses of salt containing fluid Because of the conservation of electrolytes by the kidneys, one can go a step further and assume that a surgical patient who has been on a restricted diet but who has not been losing salt abnormally will have approximately normal plasma chlorides and sodium These practical considerations are unconsciously used every day since we do not carry out plasma chloride and sodium determinations on every surgical patient

Abnormal Salt Losses—One looks among surgical patients for depleted sodium chloride when significant amounts of electrolyte containing fluid have been lost abnormally from the body by vomiting, diarrhea, drainage from intestinal, pancreatic or biliary fistulae, profuse serous or wound secretions, and prolonged sweating O'Shaughnessy,¹⁵ in 1831, recognized that in cholera important amounts of alkaline substance disappeared from the

blood and were present in the profuse dysenteric excretions Thomas Latta,¹⁶ in the same year, first administered saline solution intravenously to patients with this disease, but was discouraged with the result because the amount injected was too small, the injection was given too late, or the effect was offset by the presence of other disease. Rogers¹⁷ worked incessantly on the problem of restoring alkali deficit in cholera patients, and, in 1916, reported a reduction in the mortality of the severe cases with uremia from 111 to 27 per cent through the administration of hypertonic solutions of sodium bicarbonate and salt.

In considering intestinal obstruction it would be irreverent not to mention Hartwell and Hoguet,¹⁸ who first showed that dogs vomiting because of intestinal obstruction could be kept alive for many days if treated by large amounts of normal saline solution. Among the surgeons, the subsequent contributions of Orr and Haden¹⁹ were most important in spreading the knowledge of the abnormal chemistry of this disease.

In order to carry out the proper treatment it is important to understand the variations that occur when fluid is lost from different parts of the gastrointestinal tract. With pyloric obstruction the vomitus is predominantly acid and one finds the plasma chlorides decreased and the carbon dioxide combining power increased, giving in the advanced cases the typical chemistry of alkalosis. A satisfactory calculation of the saline solution needed for correction to normal can be made on the basis of the "clinical rule" developed by Collier, Bartlett, Bingham, Maddock and Pedersen.^{13, 20} "For each 100 mg that the plasma chloride level needs to be raised to reach the normal (560 mg per cent) the patient should be given 0.5 gram of sodium chloride per kilogram of body weight." With obstruction of the small intestine, and consequent vomiting, the loss of fluid is a combination of the acid gastric juice and the alkaline bile, pancreatic secretion and succus entericus. The resulting chemistry usually shows a low plasma chloride and a moderately reduced carbon dioxide combining power, which signifies a very definite loss of both chloride ions and base. Usually, the chloride loss is greater than the sodium loss, so it has been feasible in these cases also to use the "clinical rule" as a practical calculation of the amount of sodium chloride needed in the way of physiologic saline or Ringer's solution for correction of the water and electrolyte imbalance.

It can well be added here that when vomiting takes place in the hospital because of pyloric or intestinal obstruction, modern surgical practice requires intubation of the gastro-intestinal tract^{21, 22} and, thus, the withdrawal of the fluid and gas from the distended parts. Replacement of the water and electrolytes so removed by giving a volume of physiologic saline or Ringer's solution equal to the drainage has been found to be successful.^{13, 20, 23}

Drainage of bile from tubes in the common bile duct is an occasional source of gastro-intestinal fluid loss, and the electrolyte concentration of such bile resembles serum very closely.⁵ There are a few more basic than acid ions present, but the difference is not sufficient to make impractical replace-

ment methods calculated from the chloride loss^{13, 20} When the bile drainage is measured daily, as it should be, "volume-for-volume" replacement with physiologic saline or Ringer's solution is effective in maintaining normal blood electrolyte levels Often the required salt can be given by mouth and there is no need to administer saline parenterally

Various other methods for restoring and maintaining a normal water and electrolyte balance have been developed,^{24, 25, 26, 27} and are being put to the test of practical use All are indicative of the surgeon's desire to know more about the chemical abnormalities of the diseases under his charge and all have contributed in one way or another to the care of the seriously ill patient

Ileostomy drainage and diarrhea are not of common occurrence among surgical patients, but occasionally require attention In such cases the base loss is greater than the chloride loss, so one finds a low carbon dioxide combining power and a close to normal plasma chloride Occasionally concomitant vomiting also reduces the chlorides The pediatricians have dealt extensively with the fluid and electrolyte loss associated with diarrhea, and Haitmann²⁸ has evolved a formula for water and electrolyte correction for such cases Palmer and Van Slyke,²⁹ in 1917, developed a line chart for estimating the sodium bicarbonate required in alkali deficits

Although the surgeon is dealing chiefly with upper alimentary tract losses which generally have an excess of chloride ions and the pediatrician is at the other end of the canal and deals with excess base loss, Gamble^{2, 3, 30} has repeatedly emphasized that the same two solutions will, in the vast majority of cases, correct the electrolyte imbalance associated with losses from either end of the canal Physiologic saline solution provides the essential substances, which are water and sodium chloride ions, for the correction, while 5 per cent dextrose solution in distilled water provides carbohydrates for many purposes and an excess of freely available water for kidney function, whereby the less needed ions are excreted and correction of the electrolyte pattern takes place

Edema from Too Much Salt Solution—Edema in surgical patients has been discussed particularly by Matas,³¹ Jones and Eaton,³² Collier and his associates,^{23, 33} Ravdin and his associates,^{34, 35} Curphy and Oll,^{36, 37} and White, Sweet and Hurlwitt³⁸ It seems important here to stress that its occurrence is nearly always the surgeon's error By way of emphasizing the possible mistake, it is fitting to point out the analogy between edema in nephritis, which is so generally known, and edema in the sick surgical patient, since the conditions for both are somewhat the same

Page,³⁹ in a summary of Bright's disease, states "Most evidence does not support the belief that the ionic excretory power of the kidneys in nephrotic patients is qualitatively different from kidneys of normal persons" He further states "A number of different factors are responsible for the occurrence of nephrotic edema, the better understood and possibly more important among these being (1) Hypoproteinemia with consequent loss of

osmotic attraction of the plasma for water, and (2) the hydropigenous effect of salt in the tissues" These two factors are commonly present in the sick surgical patient, the first one may well be beyond the surgeon's control, the second is entirely in his hands The vast majority of surgical patients have merely a local lesion with no or comparatively little disturbance of their general condition On the other hand, the sick surgical patient is more seriously ill, most commonly because of one or both of two conditions—malnutrition and sepsis Frequently, also, there is hepatic and renal damage and possibly severe acute or chronic hemorrhage These factors often produce hypoproteinemia and thus predispose to the retention of water Salt comes into the picture through the frequent need for parenteral fluids by the sick surgical patient, and the surgeon's common error of administering fluids as salt solution whether sodium chloride is needed or not Thus, both in the nephritic and the sick surgical patient, there is the tendency to develop edema and all that is needed to precipitate it is sodium chloride, of which the sodium ion is the most important The dependence of generalized edema upon a supply of salt solution is worth further emphasis Shelburne and Egloff⁴⁰ produced hypoproteinemia in dogs by plasmaphoresis, and found pitting edema present without the excessive use of water or sodium chloride when the plasma proteins fell to about 3 Gm and the albumin to 1 Gm per 100 cc Then, it is important to note, large amounts of distilled water by stomach tube failed to increase the edema or the weight of the animal When sodium chloride was also given, 13 Gm per day, massive edema appeared Weech, Snelling and Goettsch⁴¹ and Lepore⁴² also emphasized that the edema associated with hypoproteinemia is a sodium chloride edema, and the general opinion is that the lower the serum proteins the less sodium chloride it takes to produce edema DeWesselow⁴³ states "Balance experiments show that approximately a liter of water is retained for every six to seven grams of sodium chloride that accumulate in the body, a normal concentration of about 0.6 per cent of sodium chloride being thus preserved in the body fluids and plasma"

Without having serum proteins down to the "critical level" of Moore and Van Slyke,⁴⁴ at which nephritics tend to develop edema, the sick surgical patient will develop edema, but generally the latter receives more salt solution Coller, Dick and Maddock³³ and Cuiphy and Orr³⁷ had several instances of this fact in their studies of edema in surgical patients

Of practical consideration is the fact that when edema is found in a surgical patient the first thought should be, "How much salt solution has this patient received and what are the serum protein values?" The surgical staff may well feel guilty when some patients come to autopsy with waterlogged tissues

Salt retention and edema have been found associated with medical conditions in which sepsis is present The best studied of these is that occurring with lobar pneumonia,⁵ there being retention during the height of the illness and an outpouring of both salt and water with the crisis Wilder and Drake⁴⁵

have warned against excess salt solution for such patients. Of the 19 infants studied by them, the three deaths that occurred were in the group of five infants who received large amounts of salt in their diet and developed extensive edema of their tissues.

In summary, it appears that the healthy individual can ingest and excrete about 35 to 40 Gm⁵ of sodium chloride a day. This limit is greatly lowered in sick surgical patients by malnutrition, sepsis, hemorrhage, profuse wound drainage, severe renal and hepatic disease, long operations, and long anesthesia, and it seems that the more pronounced these findings the greater is the retention of salt and water.

Blood Sodium Chloride Concentration No Index of Excessive Salt Retention—With the established fact that excessive salt administration in the sick surgical patient leads to edema, it would be extremely handy if the plasma chloride or sodium level would increase proportionately to the salt retained and be an index of the excessive administration. Such is not the case. In the 26 surgical patients with demonstrable edema, studied by Jones and Eaton,³² only six had plasma chlorides above the upper limit of normal of 630 mg per 100 cc,⁵ and only one was above the 700 mg level. In spite of the edema, most of the chloride values were within the normal range, but one patient had definite hypochloremia. When edema develops, the retained fluid is largely in the interstitial compartment. DeWesselow⁴³ states the fact well by saying "The result of salt retention is hydremia, rather than hyperchloremia."

The Paradox of Low Blood Electrolytes with Edema—In the previous paragraph the occurrence of hypochloremia in the face of excessive salt administration to the point of edema was mentioned. The paradox should be emphasized because it can be a trap for the unwary, and the continued attempt to raise the plasma chlorides in some instances can do the patient harm.

In our experience with quantitative methods for the replacement of lost electrolytes we noted that after having given amounts of Ringer's solution calculated from the "clinical rule" to be necessary to raise the plasma electrolytes to normal, two results occurred.²³ The patients with a recent loss of electrolytes from the vomiting of an acute illness, such as an incarcerated inguinal hernia, and whose general condition was fairly good, had a prompt return of their chemistry to normal. On the other hand, patients with a more chronic or severe illness, such as an obstructing duodenal ulcer or with peritonitis, often failed to have their blood electrolytes reach normal. These patients often had lowered plasma proteins because of malnutrition and sepsis. They excreted very little of the given sodium chloride in the urine, and they gained weight. If more Ringer's solution was given the result was simply more gain in weight. If their general condition improved, and they began to eat, then the retained water and salt readjusted, the urine output increased and the blood electrolytes rose to the normal.

A quite apparent example of the uselessness of excessive salt solution while a patient is seriously ill occurs in cases of generalized abdominal car-

cinomatosis with ascites Bartlett, Bingham and Pedersen,¹³ in our laboratory, had a good example of one such case in their study of the salt balance in surgical patients. With abdominal carcinomatosis there is usually low plasma protein because of malnutrition, and the plasma electrolytes are low because they have been taken from the blood and interstitial fluid for the formation of the ascitic fluid. An administration of saline solution parenterally to raise the plasma electrolytes generally results in only a very temporary elevation followed by a decrease and a concomitant increase in the ascites. There are other circumstances in which a similar transfer of fluid and substance is particularly harmful and at this time we wish to comment on data available from patients with severe burns.

Davidson,⁴⁶ who introduced the modern tannic acid treatment of burns, found low plasma chlorides and a retention of chlorides during the acute burn reaction and a marked urinary excretion of chlorides and water at about the time the crust was separating. Where some of this sodium chloride goes to is not difficult to answer, considering the extensive edema at the burn site, which Underhill and his associates⁴⁷ first studied extensively and demonstrated to be approximately the same as blood plasma. Blalock and his associates,⁴⁸⁻⁴⁹ and Harkins⁵⁰⁻⁵¹ studied the development of shock with such plasma losses, and also noted the extensiveness of the depleted plasma proteins. The evidence is that saline or other crystalloid solutions at the time of shock rapidly leave the vascular compartments and carry away more plasma proteins. Beard and Blalock⁴⁹ had the impression that their animals with shock died sooner if saline solution was given than if they were left alone. They state their practical opinion by saying "We do not mean to imply if a patient is in shock as the result of any injury and no donor is obtainable that saline or similar solutions should not be injected. However, in the absence of a favorable response in the blood pressure after a considerable amount of solution had been injected, almost certainly, the further administration of the same fluid intravenously would diminish the chances of recovery." The need for whole blood or plasma transfusions to treat burn shock is apparent and has been advocated by several workers.⁵²⁻⁵⁴ Trusler,⁵⁵⁻⁵⁶ Egbert and Williams⁵⁵ recently reported transfusions alone to save their experimental animals from critical burn shock.

In the shock period of the severely burned, transfusions are needed, and no more than moderate amounts of saline solution, three to four liters for an adult, are of possible value, while more may do harm. Add to this the chance that salt solution later on may cause extensive edema because hypoproteinemia and sepsis are likely to be present, then one can understand the caution to give salt solution sparingly to burn patients. We do not agree at all with the recent statement of Darrow⁵⁹ that "physiologic solution of sodium chloride, interstitial salt solution or lactate-Ringer's solution must be given in maximum amounts in extensive burns." Hypochloremia may persist in an extensive burn case even after considerable salt has been given and may lead the unwary to give more salt. Trusler, Egbert and Williams⁵⁸

reported a severe burn case in a two-year-old girl and found blood chlorides of 140 mg per 100 cc at the time of extensive general edema. This patient developed convulsions and died. Multiple transfusions saved the life of their 15-year-old burn patient, but even for her, generalized edema developed from the continued use of salt solution.

We have repeatedly pointed out that when parenteral therapy is needed, the fluid administered should be chosen to meet the needs of the individual case. When plasma proteins are low, when sepsis is present, salt solution will be abnormally retained and the resulting edema has caused the death of patients. The modern surgeon must be more than a diagnostician and an operator. He must understand the chemistry involved in his serious cases and treat the patient accordingly. Parenteral therapy is merely a means of tiding a patient over a period of crisis. There is no substitute for a good general diet and the sooner the patient is able to eat, the sooner he will get well.

BIBLIOGRAPHY

- ¹ Macallum, A. B. The Paleochemistry of the Body Fluids and Tissues. *Physiol. Rev.*, **6**, 316, 1926.
- ² Gamble, J. L. Extracellular Fluid, A Lecture Syllabus. The Harvard Medical School, 1939.
- ³ Gamble, J. L. Extracellular Fluid. *Bull. Johns Hopkins Hosp.*, **16**, 151, 1937.
- ⁴ Gamble, J. L., and Ross, S. G. The Factors in the Dehydration Following Pyloric Obstruction. *Jour. Clin. Invest.*, **1**, 403, 1924-1925.
- ⁵ Peters, J. P., and Van Slyke, D. D. Quantitative Clinical Chemistry. Vol. 1. Interpretations. Baltimore, The Williams and Wilkins Co., 1937.
- ⁶ Welch, C. S., Masson, J. C., and Wakefield, E. G. Clinical and Laboratory Findings After Excessive Loss of Intestinal Fluid from the Ileum. *Surg., Gynec. and Obstet.*, **64**, 617, 1937.
- ⁷ Freyberg, R. H., and Grant, R. L. Loss of Minerals Through the Skin of Normal Humans When Sweating Is Avoided. *Jour. Clin. Invest.*, **16**, 729, 1937.
- ⁸ Moss, K. N. Some Effects of High Temperature and Muscular Exertion on Colliers. *Proc. Roy. Soc. London*, **95 B**, 181, 1923-1924.
- ⁹ Dill, D. B., Jones, B. J., Edwards, H. T., and Oberg, S. A. Salt Economy in Extreme Dry Heat. *Jour. Biol. Chem.*, **100**, 755, 1933.
- ¹⁰ White, J. C., and Bridge, E. M. Loss of Chloride and Water from the Tissues and Blood in Acute High Intestinal Obstruction. *Boston Med. and Surg. Jour.*, **196**, 893, 1927.
- ¹¹ White, J. C., and Fender, F. A. The Cause of Death in Uncomplicated High Intestinal Obstruction. *Arch. Surg.*, **20**, 897, 1930.
- ¹² Gatch, W. D., Trusler, H. M., and Ayers, K. D. Acute Intestinal Obstruction. Mechanism and Significance of Hypochloremia and Other Blood Chemical Changes. *Am. Jour. Med. Sci.*, **173**, 649, 1927.
- ¹³ Bartlett, R. M., Bingham, D. L. C., and Pedersen, S. Salt Balance in Surgical Patients. *Surgery*, **4**, 441-461, 614-635, 1938.
- ¹⁴ Benedict, F. G. A Study of Prolonged Fasting. Carnegie Inst. Publication No. 203, 268, 1915.
- ¹⁵ O'Shaughnessy, W. B. Experiments on the Blood in Cholera. *Lancet*, **1**, 490, 1831-1832.

- ¹⁶ Latta, T Malignant Cholera Documents Communicated by the Central Board of Health, London, Relative to the Treatment of Cholera by the Copious Injection of Aqueous and Saline Fluids into the Veins *Lancet*, 2, 274, 1831-1832
- ¹⁷ Rogers, L Further Work on the Reduction of the Blood in Cholera and Sodium Hydrogen Carbonate Injections in the Prevention of Uremia *Ann Trop Med*, 10, 139, 1916-1917
- ¹⁸ Hartwell, J A, and Hoguet, J P Experimental Intestinal Obstruction in Dogs with Especial Reference to the Cause of Death and the Treatment by Large Amounts of Normal Saline Solution *J A M A*, 59, 82, 1912
- ¹⁹ Orr, T G, and Haden, R L Water and Salt Imbalance in High Intestinal Obstruction and Its Relation to Treatment *New York State Jour Med*, 30, 1161, 1930
- ²⁰ Coller, F A, Bartlett, R M, Bingham, D L C, Maddock, W G, and Pedersen, S The Replacement of Sodium Chloride in Surgical Patients *ANNALS OF SURGERY*, 108, 769, 1938
- ²¹ Wangenstein, O H, Rea, C E, Smith, B A, Jr, and Schuryzes, H C Experience with Employment of Suction in the Treatment of Acute Intestinal Obstruction *Surg, Gynec and Obstet*, 68, 851, 1939
- ²² Johnston, C G Decompression in the Treatment of Intestinal Obstruction *Surg, Gynec and Obstet*, 70, 365, 1940
- ²³ Coller, F A, and Maddock, W G Water and Electrolyte Balance *Surg, Gynec and Obstet*, 70, 340, 1940
- ²⁴ Scudder, J, Drew, C R, and Sloan, L W Anhydremia in Appendicitis *Surg Clin North Amer*, 9, 295, 1939
- ²⁵ Paine, J R, and Armstrong, W D A Study of the Fluid and Sodium Chloride Balance in Patients Treated with Continuous Suction Applied to Indwelling Duodenal Tubes *Surg, Gynec and Obstet*, 68, 751, 1939
- ²⁶ Elkington, J R, Gilmour, M T, and Wolff, W A The Control of Water and Electrolyte Balance in Surgical Patients *ANNALS OF SURGERY*, 110, 1058, 1939
- ²⁷ Scudder, J Shock Blood Studies as a Guide to Therapy Philadelphia, J B Lippincott Co, 1940
- ²⁸ Hartmann, A F Theory and Practice of Parenteral Fluid Administration *J A M A*, 103, 1349, 1934
- ²⁹ Palmer, W W, and Van Slyke, D D Studies of Acidosis IX Relationship Between Alkali Retention and Alkali Reserve in Normal and Pathological Individuals *Jour Biol Chem*, 32, 499, 1917
- ³⁰ Gamble, J L Dehydration *New England Jour Med*, 201, 909, 1929
- ³¹ Matas, R The Continuous Intravenous "Drip" *ANNALS OF SURGERY*, 79, 643, 1924
- ³² Jones, C M, and Eaton, F B Postoperative Nutritional Edema *Arch Surg*, 27, 159, 1933
- ³³ Coller, F A, Dick, V S, and Maddock, W G The Maintenance of Normal Water Exchange with Intravenous Fluids *J A M A*, 107, 1522, 1936
- ³⁴ Mecray, P M, Barden, R P, and Ravdin, I S Nutritional Edema Its Effect on the Gastric Emptying Time Before and After Gastric Operations *Surgery*, 1, 53, 1937
- ³⁵ Stengel, A, Jr, and Ravdin, I S The Maintenance of Nutrition in Surgical Patients, with a Description of the Orojejunal Method of Feeding *Surgery*, 6, 511, 1939
- ³⁶ Orr, T G Edema in Surgical Patients *Surg, Gynec and Obstet*, 63, 527, 1936
- ³⁷ Curphy, W C, and Orr, T G Edema in Surgical Patients *Surgery*, 1, 589, 1937
- ³⁸ White, J C, Sweet, W H, and Hurwitt, E S Water Balance in Neurosurgical Patients *ANNALS OF SURGERY*, 107, 438, 1938
- ³⁹ Page, I H The Genesis and Treatment of Edema in Bright's Disease *Med Clin North Amer*, 21, 1831, 1937
- ⁴⁰ Shelburne, S A, and Egloff, W C Experimental Edema *Arch Int Med*, 48, 51, 1931

- ⁴¹ Weech, A A, Snelling, C E, and Goettsch, E The Relation Between Plasma Protein Content, Plasma Specific Gravity and Edema in Dogs Maintained on a Protein Inadequate Diet and in Dogs Rendered Edematous by Plasmaphoresis Jour Clin Invest, 12, 193, 1933
- ⁴² Lepore, M J Experimental Edema Produced by Plasma Protein Depletion Proc Soc Exper Biol and Med, 29, 318, 1931
- ⁴³ DeWesselow, O L V The Variation in the Chloride Content of the Blood Internat Clin, 3, 191, 1924
- ⁴⁴ Moore, N S, and Van Slyke, D D The Relationship between Plasma Specific Gravity, Plasma Protein Content and Edema in Nephritis Jour Clin Invest, 8, 337, 1930
- ⁴⁵ Wilder, T S, and Drake, T G H Metabolism of Chloride and Total Fixed Base in Pneumonia and the Relation to Salt and Water Retention Jour Clin Invest, 7, 353, 1929
- ⁴⁶ Davidson, E C Sodium Chloride Metabolism in Cutaneous Burns and Its Possible Significance for a Rational Therapy Arch Surg, 13, 262, 1926
- ⁴⁷ Underhill, F P The Significance of Anhydremia in Extensive Superficial Burns J A M A, 95, 852, 1930
- ⁴⁸ Blalock, A Experimental Shock VII The Importance of the Local Loss of Fluid in the Production of the Low Blood Pressure After Burns Arch Surg, 22, 610, 1931
- ⁴⁹ Beard, J W, and Blalock, A Experimental Shock VIII The Composition of the Fluid That Escapes from the Blood Stream After Mild Trauma to an Extremity, After Trauma to the Intestines and After Burns Arch Surg, 22, 617, 1931
- ⁵⁰ Harkins, H N Shift of Body Fluids in Severe Burns Proc Soc Exper Biol and Med, 31, 994, 1934
- ⁵¹ Harkins, H N Experimental Burns I The Rate of Fluid Shift and Its Relation to the Onset of Shock in Severe Burns Arch Surg, 31, 71, 1935
- ⁵² Riehl, G, Jr Erfolge und Methodik der Bluttransfusion bei Verbrennungen Zentralbl f Chir, 59, 2185, 1932
- ⁵³ Riehl, G, Jr Zur Pathologie und Therapie der Verbrennung Wien klin Wchnschr, 46, 1041, 1933
- ⁵⁴ Lambret, O, and Driessens, I Le Syndrome humoro-tissulaire des brutûres étendues, Pathogenie, Traitement Rev de chir, Paris, 75, 319, 1937
- ⁵⁵ Weiner, D O, Rowlette, A P, and Elman, R Significance of Loss of Serum Protein in Therapy of Severe Burns Proc Soc Exper Biol and Med, 34, 484, 1936
- ⁵⁶ Cole, W H, and Elman, R Textbook of General Surgery New York, D Appleton, Century Co, 2nd ed, 309, 1939
- ⁵⁷ Harkins, H N Recent Advances in the Study of Burns Surgery, 3, 430, 1938
- ⁵⁸ Trusler, H M, Egbert, H L, and Williams, H S Burn Shock The Question of Water Intoxication as a Complicating Factor Blood Chemical Studies and a Report of an Extensive Burn Treated by Repeated Transfusions of Blood and Blood Plasma J A M A, 113, 2207, 1939
- ⁵⁹ Darrow, D C The Treatment of Dehydration, Acidosis and Alkalosis J A M A, 114, 655, 1940

FLUID, SALT, AND NUTRITIONAL BALANCE IN PATIENTS WITH INTESTINAL SUCTION DRAINAGE⁴

GROVER C PRINBERTHY, M D , J LOGAN IRVIN, Ph D ,

AND

R MAYO TENERY, M D

DETROIT, MICH

FROM THE DEPARTMENT OF SURGERY WAYNE UNIVERSITY COLLEGE OF MEDICINE AND THE DETROIT RECEIVING HOSPITAL
DETROIT, MICH

THE PROBLEM of fluid, mineral, and nutritional balance in patients during gastro-intestinal suction has been of great interest and has caused much concern. In fact, many discussions referring to adequate balances in surgical patients have made note of the difficulties imposed by the patient with suction drainage. Despite this fact, complete quantitative studies concerning this difficulty are hard to find. Paine and Armstrong¹ studied chloride and fluid balances in cases with gastric and duodenal suction drainage and found that there was marked loss of chloride. All authors agree that during suction drainage there is great need for careful attention to fluid and salt balance and indicate that maintenance of this balance may be effected only by parenterally administered fluids.

Since the introduction of intestinal suction drainage by the use of balloon-tipped tubes,² we have been impressed by the fact that oral administration of food, fluid, and salt is not only practical but exceedingly important in the care of patients subjected to this procedure. In addition to the advantages nutritionally, patients eating and drinking are happier and tolerate the tube more readily.

Our studies are concerned with four patients (Fig 1), two with constant suction drainage applied in the lower reaches of the ileum, and two just below the duodenojejunal fold. In all instances intubation was carried out because of small bowel distention. Of the two with the tube tip in the ileum, one (M H) had partial obstruction about a foot and a half above the ileocecal valve, the other (J K), a partial obstruction in the rectosigmoid. Of the two cases with high jejunal aspiration, one (M C) had a ruptured appendix with associated small bowel distention, the other (C J) had marked small bowel distention, the cause of which we have not been able to determine by localization or other studies. All of the cases, except the last (C J), were subjected to operation and the diagnosis confirmed.

Complete measurements of intake and output were made of all materials directly measurable and separate analyses carried out in duplicate or triplicate. None of these studies were undertaken by the routine hospital labora-

* Aided by a grant from the Committee on Scientific Research of the American Medical Association

Read before the American Surgical Association, at St Louis, Mo, May 1, 2, 3, 1940

toiy but were subjected to critical investigation in our research laboratory In order to approach the degree of accuracy we felt necessary for this study,

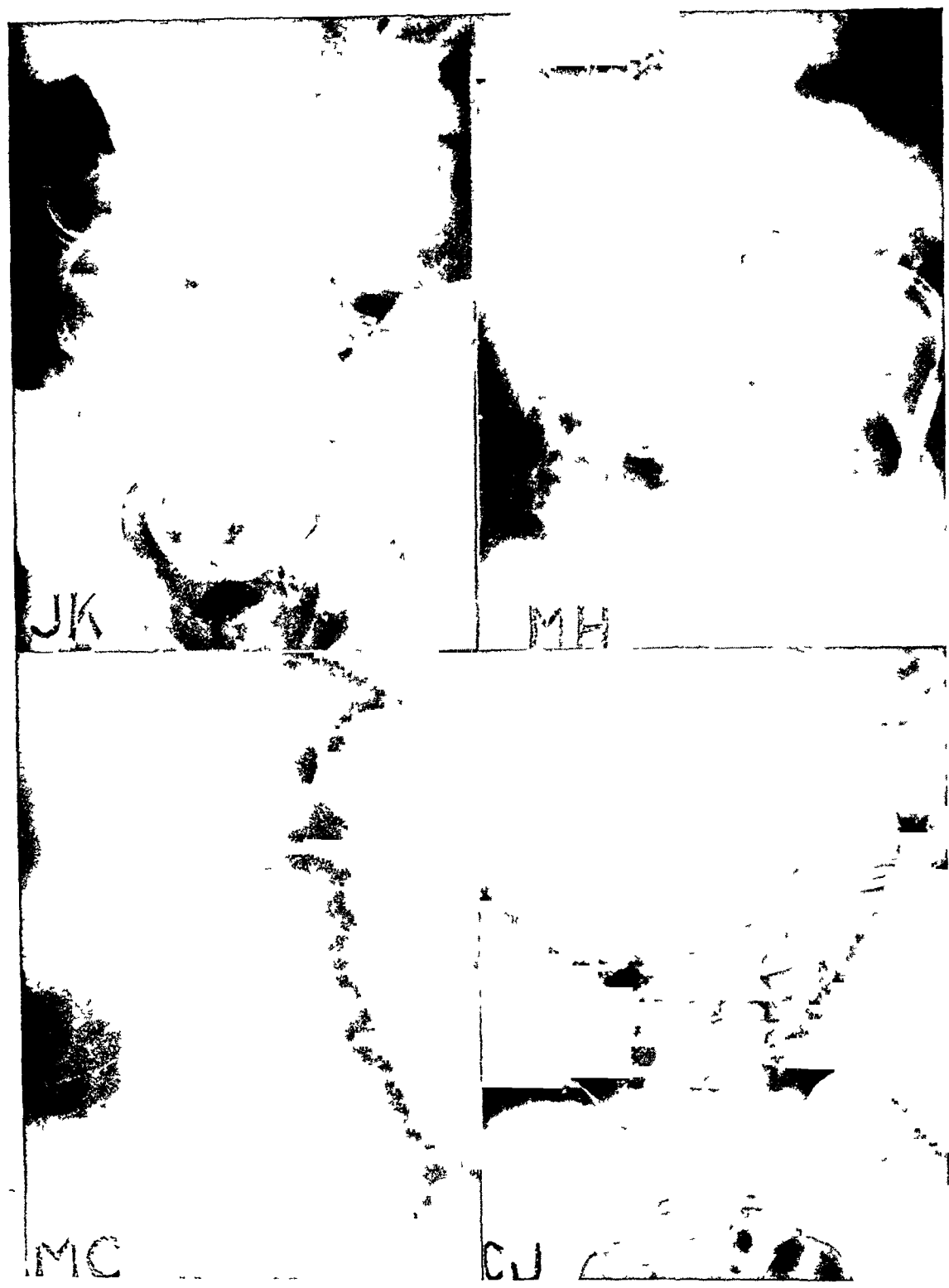


FIG. 1—Level of drainage in four cases studied, determined roentgenologically every few days

the collection of materials was made by a nurse especially assigned to this duty Intake of food was determined by weighing the diet before and after serving, and an equivalent of the food eaten by the patient weighed and

placed in a separate receptacle for drying, ashing and analysis*. No attempt was made to estimate either water of oxidation or the so-called insensible loss. Regarding the insensible loss, it is worthy of note that with the exception of one patient, for a few days, fever was not a factor of importance.

Serum protein concentrations were calculated from total nitrogen determinations by the micro-Kjeldahl method after subtraction of the nonprotein nitrogen. Carbon dioxide combining capacity of the serum was determined by the method of Van Slyke, *et al*³. The method of Wilson and Ball⁴ was used for the determination of chloride. Potassium was determined by a chloroplatinic acid procedure modified for use with a photoelectric colorimeter⁵. Sodium was determined by the method of Hoffman and Osgood⁶. All food and fecal samples were dried to constant weight in an oven at 80° C in order to estimate the water content. Samples of the dried food and feces were ashed in a muffle furnace at 400° F for the determination of sodium, potassium, and chloride. Separate samples were wet-ashed with sulphuric acid and selenium oxychloride for the determination of total nitrogen.

The simplest and most important studies for the determination of fluid balance in the usual surgical patient are obtained from a measure of the fluid taken by the patient through all routes, and that lost through urine, vomitus, suction drainage, feces, and from fistula. In addition, the volume of urine offers a fairly reliable means of estimating the degree of hydration of the patient. With patients subjected to suction drainage a comparison of the amount ingested by mouth and that aspirated by suction offers a fair estimate of the amount of fluid absorbed through the intestinal tract. Since we have been allowing patients with suction drainage to eat a full diet and drink all they desire, unless there are complications which prevent this, we have been impressed by the excess of intake over drainage in many patients. Since we allow solid food immediately the tube is at the ligament of Treitz, it has been of interest to note that even at this level the intake frequently exceeds that aspirated if the intestine has been decompressed. It is not unusual for the patient with distention to care to eat, so we are not concerned, as a rule, with too early intake of solid food. With distention present, it is rare that we note a positive balance in oral intake over materials aspirated.

In this study the oral intake as compared with the aspirated fluid in all cases revealed that varying amounts of food, fluid, and salt were utilized by the patient despite constant suction drainage. The difference between oral intake and suction drainage is markedly affected by the amount of food and fluid that the patient is able to take and the efficiency of the suction for drainage, as well as the ability of the patient to absorb the material. It is only in regard to the greater absorbing surface afforded by the length of intestine above the tube tip that low ileal drainage affords better possibilities for oral feedings. Our data show excellent nutrition and fluid balances for

* We wish to thank Mrs. Marie Diton, dietitian, Detroit Receiving Hospital, for her cooperation in determining the amount of food consumed by these patients.

NUTRITIONAL BALANCE WITH SUCTION DRAINAGE

TABLE I
FLUID BALANCE STUDIES OF J K FOR NINE DAY PERIOD
J K - FLUIDS

DATE	16-17	17-18	18-19	19-20	20-21	21-22	22-23	23-24	24-25	TOTALS
INTAKE										
BY VEIN	500	0	0	500	0	0	0	0	0	1000
BY MOUTH	3970	3820	4510	3850 +800	4100	3240 +700	4240	5000	4470	37200 +1500
OUTPUT										
BY TUBE	490	740	250	660	610	640	600	230	250	4570
BY FECES	0	0	0	500	0	500	0	0	0	1010
BY URINE	1080	1730	2460	2740	1900	2000	3000	3040	2230	20180
BALANCE										
ORAL IN - SUCTION	3480	2980	4260	3190	3490	2600	3640	4770	4220	32630
TOTAL INTAKE	4470	3820	4510	5150	4100	3940	4240	5000	4470	39700
TOTAL OUTPUT	1570	2570	2710	3900	2510	3150	3600	3270	2480	25760
TOTAL IN - TOTAL OUT	2900	1250	1800	1250	1590	790	640	1730	1990	13940
BLOOD										
HEMATOCRIT % CELLS		30.4		30.8			35.2			
SERUM PROTEIN GMS PER 100 cc		7.28		7.35			7.16			

TABLE II
CHLORIDE BALANCE STUDIES OF J K FOR NINE DAY PERIOD
J K - CHLORIDE

DATE	16-17	17-18	18-19	19-20	20-21	21-22	22-23	23-24	24-25	TOTALS
INTAKE										
BY VEIN	1770	0	0	1770	0	0	0	0	0	3540
BY MOUTH	5560	5180	3650	2580	3350	5550	3300	2780	2520	34470
OUTPUT										
BY TUBE	1890	2820	400	2380	650	2680	760	620	630	12830
BY FECES	0	0	0	300	0	60	0	0	0	360
BY URINE	910	1080	2350	4060	3180	3090	4650	2880	1930	24130
BALANCE										
ORAL IN - SUCTION	3670	2360	3250	200	2700	2870	2540	2160	1890	21640
TOTAL INTAKE	7330	5180	3650	4350	3350	5550	3300	2780	2520	38010
TOTAL OUTPUT	2800	3900	2750	6740	3830	5830	5410	3500	2560	37320
TOTAL IN - TOTAL OUT	+4530	+1280	+900	-2390	-480	-280	-2110	-720	-40	+690
BLOOD										
SERUM CHLORIDE M EQ PER LITER		107.5		115.2			105.9			

one patient with low drainage, while in the other the balances were not so good, due to smaller intake and periods of gastric distention with vomiting. In one of the cases with high jejunal suction drainage the patient cooperated so well in alimentation that he might well have been carried with little or no parenteral fluids.

During the early period of intubation, before the distention is controlled, parenteral fluids are imperative, since the patient not only is hardly likely to absorb fluid, but loses excessive fluids and salt from the gastro-intestinal tract. These studies were not made until decompression was effected and, therefore, do not indicate the losses from the intestinal tract during distention. Since the quantity of drainage from the high jejunum is frequently lower than the intake, it is obvious that aspiration is not complete, and that fair quantities pass the tube tip and are absorbed lower down. Even if we could assume that no fluid passed below the suction tip and that, therefore, the small stretch of jejunum and duodenum above the tube could absorb the quantities indicated by the difference in oral intake and drainage, we would have to account for the absorption of a much greater amount to allow for the secretion of gastric juice, bile, succus entericus, and pancreatic juice. We are, therefore, forced to the logical conclusion that even when suction drainage is effective constantly all material passing the tip is not aspirated. It is fortunate that gas is more easily aspirated than fluid. It is logical that this simple physical fact allows removal of practically all gas with a moderate amount of fluid passing the tube tip.

For purposes of brevity we are presenting one case in detail with data collected over a nine-day period. This case was the best of our series so far as balance studies were concerned during his preoperative period. He was an exceedingly cooperative patient and took fluids and food well, and we present these data to illustrate the possibility of maintaining balances without intravenous saline. It is not our custom to rely solely on oral feedings, nor, except in unusual cases, do we feel that it is good policy. We feel certain, however, that when possible, oral feedings are advantageous in that they decrease the amount of intravenous fluids necessary and offer a better means of controlling the patient.

Table I illustrates the fluid balance on this patient. It is evident that sufficient fluids were absorbed from the gastro-intestinal tract to keep the patient well hydrated and to supply more than enough fluid to excrete a large volume of urine. The drainage from the tube was minimal, and the difference between tube drainage and intake was more than is usually necessary for the average patient. The deficit between intake and output we have assumed to be insensible loss since during this period there was no evidence of retained fluid. Facilities were not available for weighing the patient accurately, so that we have no means of determining weight changes.

Table II illustrates chloride intake and output. The chloride received by vein was administered as whole blood, and the patient received no other intravenous fluid. The daily oral intake of chloride was quite sufficient to

NUTRITIONAL BALANCE WITH SUCTION DRAINAGE

TABLE III
NITROGEN BALANCE STUDIES OF J K FOR NINE DAY PERIOD
J K - NITROGEN

DATE	16-17	17-18	18-19	19-20	20-21	21-22	22-23	23-24	24-25	TOTALS
INTAKE										
BY VEIN	0 1	0	0	0 1	0	0	0	0	0	0 2
BY MOUTH	6 9	10 8	11 3	11 6	10 3	10 8	12 2	9 4	8 6	91 9
OUTPUT										
BY TUBE	1 4	1 2	1 1	1 9	1 6	1 8	1 6	0 6	0 5	11 7
BY FECES	0	0	0	0 7	0	0 2	0	0	0	0 9
BY URINE	5 3	10 1	10 3	9 5	8 6	8 7	10 4	8 5	8 2	79 6
BALANCE										
ORAL IN - SUCTION	5 5	9 6	10 2	9 7	8 7	9 0	10 6	8 8	8 1	80 2
TOTAL INTAKE	7 0	10 8	11 3	11 7	10 3	10 8	12 2	9 4	8 6	92 1
TOTAL OUTPUT	6 7	11 3	11 4	12 1	10 2	10 7	12 0	9 1	8 7	92 2
TOTAL IN - TOTAL OUT	+0 3	-0 5	-0 1	-0 4	+0 1	+0 1	+0 2	+0 3	-0 1	-0 1
BLOOD										
N P N MGMS PER 100cc		29 3		27 6			25 7			
UREA N MGMS PER 100cc		23 4		22 3			19 6			

TABLE IV
SODIUM BALANCE STUDIES OF J K FOR NINE DAY PERIOD
J K - SODIUM

DATE	16-17	17-18	18-19	19-20	20-21	21-22	22-23	23-24	24-25	TOTALS
INTAKE										
BY VEIN	1000	0	0	1000	0	0	0	0	0	2000
BY MOUTH	5490	5180	2860	2340	2550	4130	3120	2180	2200	30050
OUTPUT										
BY TUBE	1580	1450	345	2040	540	1980	670	551	576	9732
BY FECES	0	0	0	327	0	65	0	0	0	392
BY URINE	695	1120	2040	3020	2390	2520	3670	2340	1800	19595
BALANCE										
ORAL IN - SUCTION	3910	3730	2515	300	2010	2150	2450	1629	1624	20318
TOTAL INTAKE	6490	5180	2860	3340	2550	4130	3120	2180	2200	32050
TOTAL OUTPUT	2275	2570	2385	5387	2930	4565	4340	2891	2376	29719
TOTAL IN - TOTAL OUT	+4215	+2610	+475	-2047	-380	-435	-1220	-711	-176	+2331
BLOOD										
SERUM SODIUM M EQ PER LITER		147		149			154			

supply his requirements and was in excess of that lost by suction. During the entire nine-day period the total output of chloride was within 0.7 Gm of the total intake and the chloride concentration in the blood was maintained at a satisfactory level.

Sodium and potassium balances, as shown in Tables III and IV, reveal that so far as these two substances are concerned the balances are fairly well maintained on oral intake. Serum sodium levels were maintained (Table IV). The serum potassium level is of less importance and the decrease shown here is of no significance.

Of great interest are the data shown in Table V, which indicate that this

TABLE V
POTASSIUM BALANCE STUDIES OF J. K. FOR NINE DAY PERIOD
J. K. - POTASSIUM

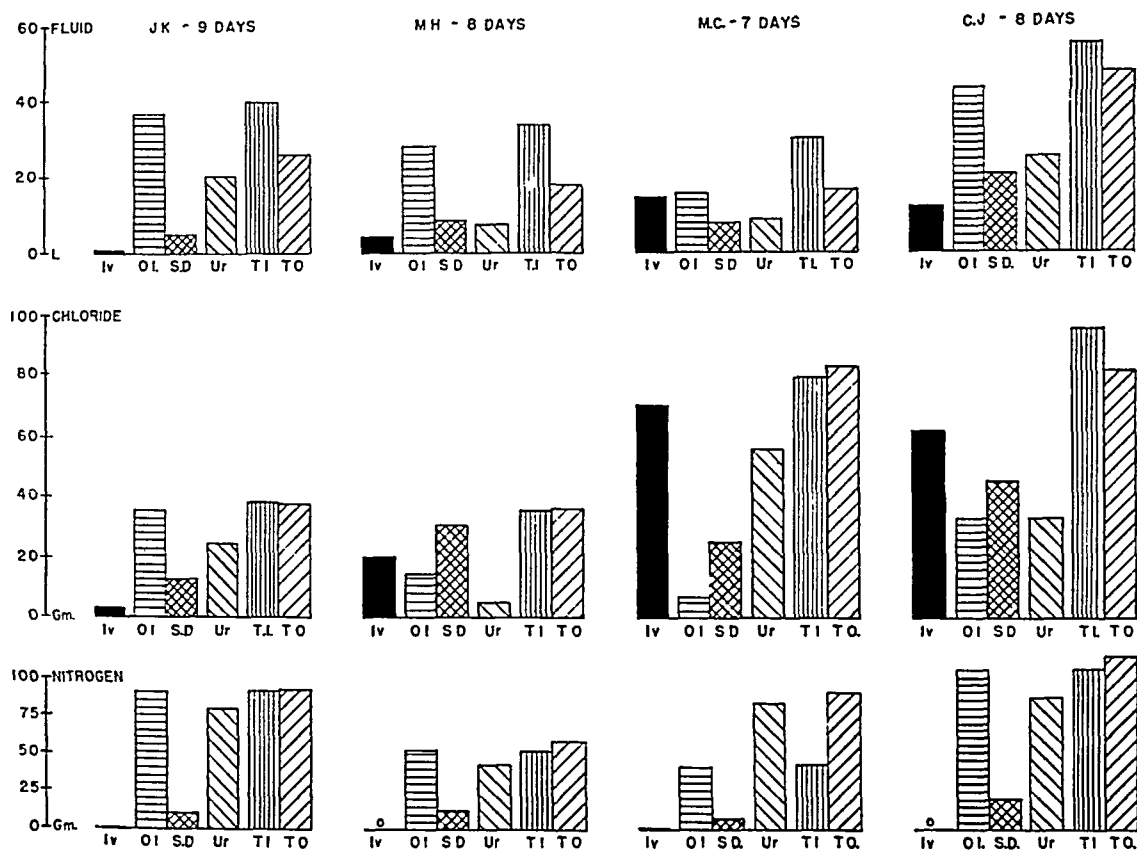
DATE	16-17	17-18	18-19	19-20	20-21	21-22	22-23	23-24	24-25	TOTALS
INTAKE										
BY VEIN	1000	0	0	1000	0	0	0	0	0	2000
BY MOUTH	750	940	1200	1000	1360	1340	1350	1070	1220	10230
OUTPUT										
BY TUBE	120	200	74	165	70	650	81	47	62	1469
BY FECES	0	0	0	380	0	80	0	0	0	460
BY URINE	810	860	1180	990	1160	1280	1570	1550	1000	10400
BALANCE										
ORAL IN - SUCTION	630	740	1126	835	1290	690	1269	1023	1158	8761
TOTAL INTAKE	1750	940	1200	2000	1360	1340	1350	1070	1220	12230
TOTAL OUTPUT	930	1060	1254	1535	1230	2010	1651	1597	1062	12329
TOTAL IN - TOTAL OUT	+820	-120	-54	+465	+130	-670	-301	-527	+158	-99
BLOOD SERUM POTASSIUM MGMS PER 100 cc		20.7		16.2			13.7			

patient has been kept in fair nutritional state so far as protein utilization is concerned. The amounts of nitrogen lost in the suction drainage are small as compared with the intake. The urinary nitrogen excretion, of which approximately 80 per cent was urea, is quite satisfactory, and with the total intake and total output of nitrogen over the nine-day period being about equal, indicates that he has utilized sufficient protein to replenish body losses of protein.

A composite graph representing the data on all four of the patients regarding balance studies of fluid, chloride, and nitrogen is presented in Graph 1. The data on J. K. are represented graphically for comparison with those from other patients. The oral intake in excess of losses by suction drainage is strikingly larger than in any of the other patients. The other patient with

drainage from the ileum (M H), whose oral fluid intake-output difference ought to have been sufficient to maintain fluid balance, appeared slightly dehydrated regularly, and the urine volume was quite low. Intravenous sodium chloride was given this man and it is interesting to note that his chloride balance was good. He lost a large amount of chloride in his drainage and sufficient chloride was given by vein to correct this. However, despite the fact that the total intake of chloride was almost as great as the total output, the excretion in the urine was quite small, and this man could

INTAKE - OUTPUT SUMMARY



GRAPH I—Composite graph showing fluid, chloride, and nitrogen balances in four patients studied

have had more intravenous salt as well as glucose solution with advantage. The reason for his low intake of chloride was that he took food poorly and his intake consisted in large part of water and on several occasions the patient vomited because his stomach dilated after aerophagia. This also accounts for his low protein utilization which resulted in a negative nitrogen balance, which indicated that he was not well maintained nutritionally despite the fact that the tube was in the lower ileum. In addition, the low daily excretion of nitrogen attests to the fact that we were not able to maintain nutrition. However, the amount of protein which he did utilize from his oral intake was of definite advantage in that it did provide him with some protein which he would not have had without oral feeding.

In regard to the two patients (M C and C J) with high jejunal drain-

age, the high level might suggest that oral intake would be of little consequence in maintaining the patient in fluid and nutritional balance. That this was to some extent our concept is illustrated by the fact that large quantities of intravenous fluids were administered. Either of these patients might have been maintained on smaller quantities of intravenous fluids to some advantage. In both these cases with jejunal suction about half their fluid intake was aspirated. C J had a much greater intake of fluid than M C and accordingly absorbed more fluid from his intestinal tract. The urine output on M C was well over a liter daily, and C J excreted excessively large amounts of urine, averaging almost 3,000 cc daily. The difference between total intake and output, which might be assumed in both instances to be insensible loss, was much less in C J than in M C. Since the serum protein level of C J was 8.3 at the beginning of the study and dropped to 7.1 shortly after, it might be assumed that this was the result of replacing fluids lost during dehydration. However, the serum chloride was not abnormal. In both M C and C J the amount of chloride lost in suction was greater than that taken by mouth, and despite the low urine volume of M C her chloride excretion was quite large. Since M C was a female and urine and feces were grouped together, this might be suspected of accounting for the high value for urinary chlorides. Fecal studies on other patients indicate that this was not so, but that the urine was more concentrated. Both these patients received more intravenous saline than should have been given, and while they were capable of excreting large amounts of chloride, it would have been better had we given a portion of the intravenous fluid as glucose in water. It is to be noted that while M C excreted slightly more chloride than she ingested, C J actually retained chloride despite the fact that there was no noticeable edema. A portion of this might be accounted for in retained feces since no attempt was made to clean the lower bowel at the beginning and end of the study. Nitrogen balance was not maintained in either of the patients with jejunal suction. This was to be expected in M C, whose protein intake was not great, and the patient had a moderate amount of fever for a few days. In C J, however, the difference between intake and suction drainage was adequate and a better balance should have resulted. We are at a loss to explain the poor balances on C J but we feel fairly certain that these were not due to the most obvious possible fault, that of measuring, since the discrepancies are not always in the same direction.

These data indicate that in patients with low ileal drainage it is possible to maintain good fluid, salt and nutritional balance if the patient ingests a sufficiently larger quantity of food, salt, and fluid than is removed by suction. However, even in cases with drainage from the lower ileum this should not be relied upon entirely. When suction is exerted at higher levels it is much more difficult if not impossible to maintain good balances, especially as regards salt. The amount of material which can be absorbed by the gastrointestinal tract in cases decompressed by suction drainage is of decided

advantage in maintaining the patient in good fluid, salt, and nutritional balance. The use of parenteral fluids in conjunction with oral intake in excess of suction drainage is important.

We recognize that with variations in the amount of suction drainage from patient to patient, four patients are not sufficient to draw broad conclusions concerning balances. We are, therefore, presenting this material as a preliminary report and are continuing this study.

We wish to thank Dr. Charles G. Johnston, Professor of Surgery at Wayne University, under whose direction this study was carried out, for cooperation and guidance.

REFERENCES

- ¹ Paine, John P., and Armstrong, Wallace D. *Surg., Gynec. and Obstet.*, **68**, 751-759, 1938.
- ² Abbott, W. Osler, and Johnston, Charles G. *Surg., Gynec. and Obstet.*, **66**, 691-697, 1938.
- ³ Van Slyke, D. D., and Cullen, G. E. *Jour. Biol. Chem.* **30**, 289, 1917.
Van Slyke, D. D. *Jour. Biol. Chem.*, **30**, 347, 1917.
Van Slyke, D. D., and Stadie, W. C. *Jour. Biol. Chem.*, **49**, 1, 1921.
- ⁴ Wilson, D. W., and Ball, E. G. *Jour. Biol. Chem.*, **79**, 221, 1928.
- ⁵ Tenery, R. M., and Anderson, C. E. *Jour. Biol. Chem.*, **135**, 659, 1940.
- ⁶ Hoffman, W. S., and Osgood, B. *Jour. Biol. Chem.*, **124**, 347, 1938.

DISCUSSION—DR. WALTERMAN WALTERS (Rochester, Minn.) When, a few weeks ago, I discussed with my colleague, Doctor Snell, the possibilities of contributing to this very excellent group of papers, he said that if I expected in five minutes to contribute anything to what a high-pressure biochemist like John Peters had a chance to say in 20 minutes, I was crazier than he thought I was. So my discussion is really going to revolve around a discussion of some of the clinical aspects of dehydration toxemia rather than physiologic chemical studies in such cases.

I thought that Doctor Peters in his presentation of his charts, particularly that first one, very clearly showed that there are clinical evidences of dehydration toxemia, which sometimes occur before the chemical changes become marked, and I refer particularly to the evidence of the decrease in urinary output in cases with dehydration toxemia.

It seems that the interesting thing, also, in such cases is that one sees the red cheeks of such patients due to the alkalosis, the dry skin and tongue, and in addition the blood pressure usually is found to be below normal. I think it is worth while to call attention to these clinical evidences of dehydration toxemia, because in many instances the cooperation of men skilled in biochemical tests is not available and if, therefore, one recognizes the possibility of dehydration, it can be compensated for.

I was very much interested in what Doctor Maddock had to say regarding the administration of too much salt solution and the development of edema which occurred as a result. One sees that, fortunately, infrequently. If one does not administer a total of more than 1,000 cc. of normal saline above the amount of fluid excreted, regardless of whether the patient has an obstructing lesion of the gastro-intestinal tract or biliary tract or a fistula, in other words if a positive fluid balance of 1,000 cc. is maintained, that 1,000 cc. being administered as normal saline, the patient usually does not experience edema that is due to chloride retention.

On the other hand there is equal danger in administering hypertonic solu-

tions of glucose to patients to whom one does not want to administer too much salt, and, as Doctor Peters emphasized in his discussion, that water and food given orally in the presence of gastro-intestinal obstruction will frequently cause a depletion of chlorides, similarly hypertonic glucose solution intravenously injected will produce in some cases depletion of chloride when injected too frequently, especially if a biliary fistula is present. I recall such a case. A man, who had obstruction of the common bile duct as the result of a stone, was given glucose because of diabetes but in too large a concentration, and although insulin was given to metabolize the glucose, a depletion of chlorides developed. The clinical evidence of this condition was rather marked owing to the incoherent remarks which the patient would make in discussing his progress. Also, the blood showed a decrease in the chloride.

In the symposium, no reference has been made to the physiochemical changes which occur as a result of the loss of fluids and electrolytes through biliary and intestinal fistulae. I recall a case of external biliary fistula in which a tremendous amount of bile was lost on the seventh and eighth days following operation, with a low urinary output which you will recall I mentioned as clinical evidence of dehydration. A tremendous amount of total chloride was lost in the bile, more than six times the normal, and there was a marked reduction of the urinary base. With the administration of 22 Gm of sodium chloride and 20 Gm of sodium lactate daily for six days, there was a normal excretion of base in urine and bile and a decrease in the excretion of sodium chloride in urine and bile to normal limits and, coincidentally, a tremendous decrease in the amount of bile excreted externally (Table I).

TABLE I
CHLORRHEA LOSS OF BASE AND CHLORIDE

Days Postopera- tively	Output, Cc		Chloride, Gm		Base	
	Bile	Urine	Urine	Bile	Urine*	Bile*
7 and 8	6,710	810	0 38	50 2	0 4	9 4
9	4,000	1,070	1 9	28 9	0 7	5 6
9 to 15	22 Gm of sodium chloride and 20 Gm of sodium lactate were given daily					
13	1,070	2,090			2 3	1 5
14	1,130	1,830	7 2	8 1	2 4	1 5

*As liters of tenth normal base

Whether or not this was due to the administration of chloride is debatable, in view of the marked reduction in the external drainage of bile which probably was the most important factor concerned. This, I think, is of particular importance, because if one keeps track of the fluid obtained through suction apparatus or lost in vomitus and in the urine, one frequently has a good indication of progress, provided that a 1,000 cc positive fluid balance is obtained.

Another way of supplying the necessary fluids and electrolytes to patients who experience postoperative obstructions, particularly those in connection with gastro-intestinal anastomosis, is by the performance of jejunostomy. In one case which I recall, a tremendous loss of fluid occurred as a result of obstruction at the gastrojejunal stoma following a Polya-type of resection. An elevation of the blood urea and a drop in the blood chloride occurred. By the performance of jejunostomy, under local anesthesia, although the excre-

tion of fluid by the stomach continued high, physiochemical balance was kept under control for food, electrolytes and fluid could be administered through the jejunostomy tube until the site of anastomosis opened. About three years ago I reported seven cases of this type, in which the inflammation subsided in periods ranging from 28 to 36 days with gastro-intestinal continuity carrying on satisfactorily.

I recall another case of a similar type, in which obstruction occurred following gastrojejunostomy for duodenal ulcer. There was a characteristic rise of the concentration of blood urea and a fall in the blood chlorides as a result of the loss of fluids by vomiting. With jejunostomy, physiochemical balance was maintained and the lumen at the site of gastrojejunostomy opened on the fortieth day. It has been our experience, too, in cases of this type that sometimes when large amounts of fluid such as glucose are injected intravenously they may be excreted into the stomach, and I believe that occasionally I have smelt the glucose in the gastric secretion when the fluid was excreted that way.

I think that this symposium has been an excellent one. I do think that we must not overlook the clinical factors in estimating progress in these cases. I believe that sometimes we give too much fluid in such cases and that a positive fluid balance of 1,000 cc. is usually adequate.

DR OWEN H. WANGENSTEEN (Minneapolis, Minn.) This has been a most interesting and profitable discussion, I am sure, for all of us. I am pleased to note that into this discussion have come reservations concerning overdeluging the patient with fluid, as well as references to thwarting dehydration and dechlorination. All of us who deal with the practical aspects of these problems on the wards may fall into both types of error.

The work of Collier and Maddock, and their associates, on the fluid requirements of patients has focused the eyes of surgeons on the great importance of adequate orientation in these particulars. The paper by Doctor Peters, I think, is of great practical importance to the surgeon and we shall all look forward to the opportunity of studying it when it appears in print. Quite properly, Doctor Peters placed considerable emphasis on the matter of distention as related to the absorption of fluid and to the prophylaxis of distention after abdominal operations. He referred to the work of one of my associates, Dr. Clarence Dennis, who demonstrated that the placement of water on the exposed ileum of the dog may cause ulceration of the mucosa. Dennis, however, was unable to produce similar changes by the placement of water on the gastric mucosa of the dog. Doctor Peters' suggestions concerning the oral administration of water to postoperative surgical patients are interesting. It may be that the oral administration of saline solution is preferable. However, I find it difficult to get patients after operation to ingest more than half a liter of saline solution unless the salt is given in capsules. Patients do enjoy the refreshment of cool water.

With reference to Doctor Peters' remarks upon the prophylaxis of distention, I would like to point out that, together with Dr. Charles Rea of my department, it was observed that the swallowed air factor was a most significant item in the establishment of intestinal distention (Surgery, 5, 327, 1939). In dogs, with transection of the cervical esophagus, the proximal end opening at the skin, the distal end being closed, it was found that such dogs tolerated complete ileal obstruction unusually well. One such dog survived for 57 days, dying ultimately of starvation. There was no distention at autopsy. The swallowed air factor having been excluded by esophagostomy, the bowel was able to reabsorb the secretions dumped into the intestinal

canal—namely, gastric juice, bile, pancreatic juice and succus entericus. When, however, the distal end of the esophagus in the neck was left open, the dog aspirated air into his stomach, the intestine dilated with the establishment of ileal obstruction, and the animal did not survive the distention long. This occurrence emphasizes the great importance of prophylaxis of intestinal distention described by Doctor Peters.

Most of the discussion in this symposium has hedged about the item of control of the patient throughout the operative period. I might, therefore, say something about the matter of the early care of the patient after operation. A common error among surgeons is failure to fully appreciate the profound effect of severe operation and prolonged anesthesia upon the loss of fluid by sweating. Anesthesia, whether local, regional or general, causes a dilatation of the capillaries of the skin with consequent loss of large amounts of fluid. The salt content of this fluid averages probably about 3 Gm per liter. The oliguria which patients present the day following operation, not infrequently finds its explanation in the failure on the part of the surgeon to reckon adequately with the loss of fluid through this source. Whereas there are satisfactory means of determining whether patients are adequately chlorinated the most practical of available means of knowing whether a patient is hydrated adequately are the absence or presence of thirst and a satisfactory output of urine. Overchlorination of patients is frequently responsible for oliguria. I have come to feel that the loss of fluid through perspiration is so important that our nurses on surgical floors try to compute roughly the fluid loss through this source in terms of 1, 2, 3 or 4 plus. For a patient who has had a protracted operation under anesthesia, and who has not lost large quantities of fluid from the gastro-intestinal canal, 5 Gm of sodium chloride and 3,000 to 4,000 cc of fluid will usually suffice, and insure a satisfactory urine output, during the first 24-hour period.

In patients in the older age-group (over 60), we have returned largely to the subcutaneous route of administering fluid. It has been shown, even in young sturdy patients with good cardiac reserve, that intravenous injection of fluid at the rate of 15 cc per minute will accelerate the heart rate. Patients with malignancies in the upper age-brackets not uncommonly have coronary sclerosis with diminished cardiac reserve. Intravenous administration of fluid to such patients not uncommonly elicits cardiac pain and may provoke pulmonary edema. I have come to insist on the subcutaneous administration of fluid to such patients and find it eminently satisfactory.

A number of my associates and I have been interested in the matter of attempts at maintaining patients with obstruction in the upper digestive tract in nitrogen equilibrium. Up until now, surgeons have concerned themselves solely with the item of proper water and electrolyte balance and the administration of enough glucose to prevent ketosis. Why not also, maintenance of patients in proper caloric and nitrogen balance?

Our plan in patients presenting obstructions (cancer or ulcer) at the gastric outlet is to avoid jejunostomy or preliminary gastrojejunostomy. Such a patient may be maintained in satisfactory water, electrolyte, caloric and nitrogen balance, and operated upon after satisfactory preparation, as though he were not obstructed. Five hundred cubic centimeters of human plasma daily usually suffices to maintain nitrogen equilibrium. A similar amount of whole blood will not maintain a patient in positive nitrogen balance. Recent experience with the intravenous administration of amino-acids (F. Stearns & Co., Detroit) suggests that this is a simple and practical manner in which to supply patients with a source of nitrogen when the gastro-intestinal canal is not available for feeding. I like to have patients who can not take protein by

mouth get about 40 grams of protein intravenously. Satisfaction of fluid, glucose and mineral requirements is not enough. Clinical trial shows that patients with a deranged gastro-intestinal canal do better when the patient is maintained in nitrogen equilibrium as well.

During the past year, we have been probing the feasibility of administering bovine plasma to man intravenously. In a preliminary communication on the subject (*Proc Soc Exper Biol and Med*, 43, 616-621, 1940), it has been indicated that bovine plasma may be given to man in fairly large quantities. We observed that bovine plasma so administered was retained and was not excreted in the urine, it is our impression that it is retained and metabolized. The largest amount that has been given any single patient is 1,500 cc. Our observations to date are not numerous, but more than 50 patients have received bovine plasma in quantities of 100 cc or more intravenously. There have, of course, been some reactions. We have had only one anaphylactoid reaction, in an asthmatic. There have been no deaths. Much remains to be done to establish the practicability of the method for general clinical use. My surgical associates and I are hopeful that the method may become useful in the treatment of shock and contracted protein stores in man, both in civil and war surgery. It is not unlikely that separation of the albumin and globulin fractions may pyramid the usefulness of the method, for the globulin fraction appears to be the more toxic. However, to date, we have had more success (less reactions) with the administration of whole bovine plasma than with albumin fractions alone. Surgeons must give more thought to the matter of maintenance of nitrogen equilibrium in obstructed as well as debilitated patients.

DR JOHN P. PETERS (New Haven, Conn., closing). It is only when I am among surgeons or physicians that I am ever flattered by being called a high-powered chemist. Chemists know me. I mention this because I did not mean to neglect emphasis on the clinical aspects of these cases, although I know I was a little hasty to get over to the chemical side. I mentioned, especially in my last words, that you need not worry much about the patient who is excreting 1,000 to 1,500 cc of urine or more a day. I think if more attention were given to this we would not have to do quite so much blood chemistry, and often make so many mistakes in giving fluids.

Now I want to speak a moment about this business of excessive chloride. I agree that one should not give enormous amounts of chlorides and that often a great deal too much is given. I think it is a mistake, also, to give this chloride in many instances intravenously, especially in the light of Doctor Blalock's studies, in which he shows that, in this way, in patients with shock you can wash protein out of the blood. My own practice is to administer saline chiefly under the skin, as Doctor Wangenstein has suggested, and to reserve the vein for hypertonic glucose, if it is necessary. I say hypertonic. I prefer to use 10 per cent to get it into a small volume, and I give that intravenously because glucose under the skin is irritating and withdraws fluid from the blood stream at least temporarily.

Doctor Maddock spoke, in his cautions, of edema occurring with hypochloremia or low chlorides. I think that this is quite common. I am not sure that the presence of the hypochloremia itself may not bring about such disorganization of the body as to provoke the edema. In many of these cases, one need not encounter all the difficulties that Doctor Maddock has spoken of if small amounts of hypertonic saline are given to overcome the salt deficiency in the plasma and bring the osmotic pressure of the plasma

up to normal We give 2 per cent saline in relatively smaller volumes than we would normal saline to these cases, sometimes with very good results

I believe that attention to the electrolyte pattern and administration of salt according to the disturbances in this pattern, with due regard to the presence of edema and excessive hydration when it occurs, may obviate these difficulties and better the care of the patients

DR JOHN SCUDDER (New York, N Y, closing) I should like to ask a question Has Doctor Peters ever seen a case passing two or three liters of urine and yet dehydrated? When the total ionic content of the blood is decreased in Asiatic cholera, and a severe case of intestinal obstruction, and you give a physiologic salt solution, you have not enough base to retain that fluid and the person puts it out Have you seen that type of case in severe burns? We have had cases passing 2 or 3 liters of fluid, but yet if you make studies of their blood it will be found to be concentrated If you determine the salt content, you will find that their total base is decreased Gamble has brought up the question that you cannot retain water unless you have sufficient base In cases of base depletion will you not have an excess of urine output if you do not administer enough base?

DR JOHN P PETERS (New Haven, Conn, closing) You are more likely to have it in these cases than you are in patients with gastro-intestinal disturbances, of which I especially spoke I, perhaps, should speak a moment here about the problem of burns and infections It is quite well recognized that in pneumonia and certain pulmonary diseases and other highly febrile conditions, there is a tendency for individuals to keep the concentration of base continually low in the serum Under those circumstances they will dehydrate themselves because they will waste salt if you do not give it to them On the other hand, if you give excessive salt in the presence of conditions of this kind, you are not always able to restore the salt concentration in the serum to normal, even if you push it to the point of giving these patients edema The mechanism of this is not clear yet, but in pneumonia there is a tendency to waste salt in the urine and to waste fluid with it, and to maintain a relatively low concentration in the serum This may have a particular bearing on the problem of burns

DR WALTER G MADDOCK (Ann Arbor, Mich, closing) I should like to emphasize, further, a difference in the response of surgical patients, depending upon their general condition, to the administration of sodium chloride solutions given according to our "clinical rule" to correct electrolyte deficiencies The patients who have had a recent or acute loss of electrolytes, such as would occur from vomiting due to an incarcerated hernia, and whose general nutrition is good, usually, after their operation and saline solution administration, have a prompt return of their plasma electrolytes to normal

The second group are the patients who have a chronic illness producing malnutrition or who have the other conditions of the sick surgical patient such as sepsis, significant renal and hepatic damage or severe acute or chronic hemorrhage When given calculated amounts of saline solution to correct an electrolyte deficiency, the correction for these patients is often incomplete An occasional one will excrete quite an amount of sodium chloride in the urine, and this loss will account for the failure of the plasma electrolytes to reach normal The majority, who show only a partial return of their plasma electrolytes to normal, do so, we feel, because more than usual of the saline solution goes to the interstitial spaces Attempts to raise the plasma electro-

lytes by giving more salt have simply resulted in more weight gain, so we have abandoned this attack. We feel that the first administration of salt by the "clinical rule" provides sufficient electrolytes for correction of the deficit, and it has been our experience that if the patient's general condition improves, if he begins to eat, then the excretion of water and sodium chloride in the urine increases, there is some loss in weight, and the plasma electrolytes come up to the normal level.

For the vast majority of general surgical patients the handling of the electrolyte problem by the "clinical rule" for restoration and the "volume-for-volume" replacement for maintenance has been a working procedure in the hands of our resident staff without the frequent use of expensive chemical studies.

DR R. MAYO TENERY (Detroit, Mich., closing). Doctor Peters mentioned that patients with gastro-intestinal suction do better if he gives them either nothing by mouth or only normal saline by tube. We believe that it is better to give food to patients with long tube suction, as they are then much happier and nutrition can be kept up very well.

Graph 1 shows that an appreciable amount of dietary nitrogen was absorbed and utilized by all four patients. M. J. did not absorb enough to keep up a good balance, but she was better off than if she had been given no nitrogen by mouth.

Our long-tube diet consists of almost any food except that having a high fiber content. When the tube is in the lower ileum, patients can keep up good nutrition if they take an adequate diet, and very few of them need much in the way of intravenous fluids. Of the two patients with upper jejunal suction, each had a negative chloride balance, as far as their oral intake compared to suction drainage was concerned, but they did take in more nitrogen and water than was removed by tube.

Thus, we feel that food makes our patients more comfortable and maintains their nutrition much better than if they were given nothing by mouth.

A CLINICAL STUDY OF THE PLASMA VOLUME IN ACUTE INTESTINAL OBSTRUCTION*

JACOB FINE, M D , ALFRED HURWITZ, M D ,

AND

JEROME MARK, M D

BOSTON, MASS

FROM THE SURGICAL DEPARTMENT OF THE BETH ISRAEL HOSPITAL AND THE HARVARD MEDICAL SCHOOL BOSTON MASS

IN EXPERIMENTS on animals with uncomplicated obstruction of the small intestine a fall in the volume of circulating plasma sufficient to account for the death has been observed¹ The evidence is clear that this loss of plasma may occur in the absence of dehydration or the accumulation of significant quantities of fluid in the cavity or wall of the intestine or in the peritoneal cavity² Moreover, the intravenous administration of large amounts of fluid and electrolytes does not prevent the decrease in plasma volume, whereas the intravenous injection of an equal or smaller volume of plasma not only maintains the plasma volume but prolongs the life of the animal³ Decompression, as might be expected, halts the loss of plasma and may even permit substantial recovery of the fraction lost⁴ Desoxycorticosterone acetate also prevents the plasma loss, if given early, and may increase the volume above normal⁵ Finally, distention of the colon and of the gallbladder does not cause a significant plasma loss while distention of as little as two feet of small intestine may do so⁶

The purpose of this communication is to present clinical evidence confirming some of these experimental findings

Case 1—A 40-year-old man with an indirect inguinal hernia, but otherwise in good health, was subjected to a repair of the hernia After two uneventful postoperative days he gradually became distended Enemata were ineffectual Periumbilical colic and vomiting followed Gastric lavage was necessary When the abdomen was much distended and tense, a roentgenogram showed many distended loops of small intestine (Fig 1) At this time the plasma volume was 2,414 cc† Thirty-six hours after the introduction of a Miller-Abbott tube the distention largely disappeared and the plasma volume rose to 3,408 cc, an increase of 994 cc

COMMENT—This is presumably an instance of transitory mechanical rather than functional ileus If the plasma volume after decompression is regarded as the normal for this patient, it is apparent that intestinal obstruction resulted in a loss of plasma of 30 per cent It is significant that this loss of plasma occurred in spite of the administration of large amounts of fluid, it was corrected only by decompression

* Read before the American Surgical Association, St Louis, Mo, May 1, 2, 3, 1940

† All plasma volumes were measured by the method of Gibson and Evelyn⁷ on admission or at least several, and usually, about 12 hours after parenteral fluids were stopped, so that very little of the recorded volumes can be regarded as due to hydremic plethora

Case 2—A woman, age 78, entered the hospital with nausea, vomiting and obstipation of four to five days' duration. On admission she was found to have auricular fibrillation and a markedly distended, tense abdomen with visible peristalsis. A roentgenogram of the abdomen showed extreme gaseous distention of loops of small intestine and a calcified gallstone in the lower ileum (Fig 2). The plasma volume was 2,020 cc. Because of her precarious condition nonoperative decompression by the Miller-Abbott tube was attempted, but without success owing to her refusal to cooperate. One hundred per cent oxygen inhalation was then tried, again without success for the same reason. Eight hours after admission the plasma volume had fallen to 1,661 cc. Surgical intervention followed immediately. The gallstone was removed and an enterostomy tube was inserted. Eighteen hours later abdominal distention had decreased considerably, and the plasma volume was 2,562 cc, an increase above the previous measurement of 900 cc. A roentgenogram two



FIG 1—Case 1. Transitory postoperative mechanical obstruction of 36–48 hours' duration. Moderate distention. Plasma loss 29 per cent. Plasma gain after decompression 41 per cent.



FIG 2—Case 2. Gallstone obstruction of ileum of four days' duration. Extreme distention. Plasma loss 45.5 per cent. Plasma gain after decompression 83.5 per cent. Arrow points to gall stone.

days later, however, still showed some loops distended with gas. On the fifth postoperative day the plasma volume had risen to 3,048 cc. A roentgenogram on the sixth postoperative day showed almost complete deflation.

COMMENT—The very low plasma volume observed just before operation and the final increase of 83.5 per cent following effective decompression are in conformity with the experimental finding that the plasma volume falls during distention and rises following decompression.

Case 3—A 29-year-old male was operated upon for recurrent right lower quadrant pain, nausea and vomiting of several months' duration. Several loops of ileum were found adherent to one another by numerous adhesions, which were divided. Nausea and vomiting recurred a week later and again two weeks later. On this last occasion food and fluids by mouth could not be retained, constipation was complete and distention appeared. A roentgenogram showed many distended loops of small bowel containing fluid

levels The plasma volume was 2,494 cc Four days later, after effective decompressive procedures, the plasma volume was 3,339 cc, a gain of 34 per cent above the previous measurement

COMMENT —The magnitude of the plasma volume change in this patient was less than in the two preceding patients perhaps because the degree of gaseous distention was less marked

If it is true that the general physiologic disturbances in uncomplicated intestinal obstruction are due to the resulting distention rather than to the obstruction *per se*, one should expect to find the same constitutional changes when severe distention of nonobstructive origin is present In support of this inference we present the following case

Case 4 —An obese female, age 42, was operated upon for a large papillary cystadenocarcinoma of the left ovary She was immediately placed on one of a group of post-operative diets which are being studied to evaluate the distending capacity of different types of foods On the first postoperative day the abdomen became tense, distended and tympanic The following day the distention was extreme, nausea and vomiting occurred and nothing could be passed by rectum, even with the aid of repeated enemata The plasma volume was 2,531 cc By the use of an intragastric tube, hot stupes, more enemata and a change in diet to what we believe are nondistending foods, complete deflation resulted, after the subsequent three days On the sixth postoperative day the plasma volume rose to 4,221 cc

COMMENT —If this final measurement be taken to represent this patient's normal plasma volume, the distention may be considered to have caused a 40 per cent loss in circulating plasma, or, stated the other way, the decompression caused a gain of 67 per cent in circulating plasma This is indirectly reflected in the accompanying change of 21 per cent in the hematocrit (Table I—Case 4)

A similar, though less striking, observation was made in the following case

Case 5 —A 65-year-old man became increasingly distended following suprapubic cystotomy and bilateral vasectomy for obstructing prostatic hypertrophy On the fourth postoperative day the abdomen was enormously distended and tympanic, audible peristalsis was absent and a roentgenogram showed marked gaseous dilatation of the small intestine The plasma volume was 2,868 cc Following the institution of gastric suction, 100 per cent oxygen inhalation, enemata and heat to the abdomen for 24 hours, the distention decreased On the following day after an effective bowel evacuation the distention disappeared Four days later the plasma volume was 3,725 cc, which represents a gain of 29 per cent

COMMENT —Since the disturbance in this and in the previous instance was clearly one of adynamic ileus, it is apparent that the plasma loss in ileus, whether of mechanical or functional origin, is due to the distention common to both In the light of this observation, severe distention even of functional origin, may become a vital matter

The degree of dilatation of distended loops as seen roentgenologically or as suggested by the increase in size of the abdomen does not necessarily indicate the degree of intra-intestinal pressure, which is responsible for the loss of plasma Such objective signs may, therefore, not always be relied upon as a

guide to the extent to which plasma is being lost. Consequently, even when the roentgenograms of two different patients show comparable degrees of dilatation, the extent of the plasma loss may differ considerably. Thus the roentgenogram in the following patient showed greater gas accumulation in the small intestine than in Case 1. The plasma loss, however, as will be seen below, was less in spite of the longer duration of the obstruction.

Case 6—A 72-year-old woman with a history of a lower abdominal operation 14 years previously, entered the hospital complaining of intermittent, periumbilical colicky pain, nausea, constipation and increasing distention of four days' duration.



FIG 3—Case 6. Mechanical obstruction of ileum of four days' duration. Marked distention. Plasma loss 25 per cent. Plasma gain after decompression 33.8 per cent.

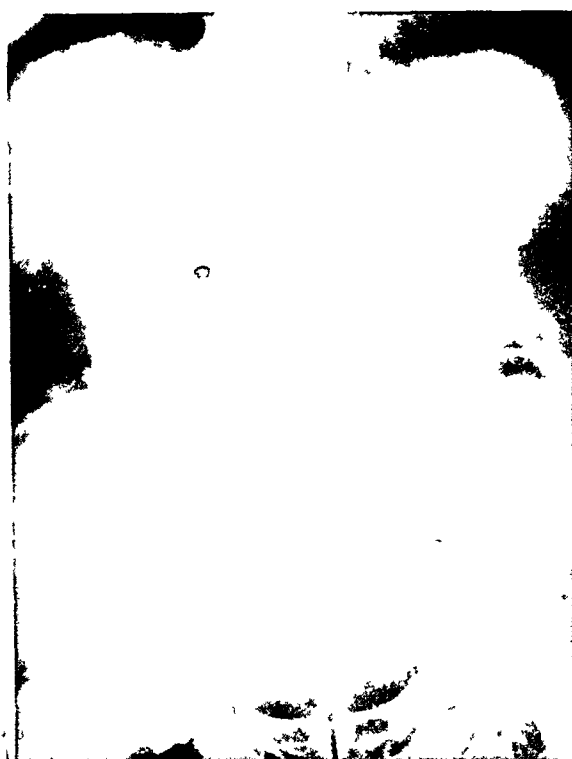


FIG 4—Case 7. Strangulation of loop of ileum in femoral hernia probably of four days' duration. Traces of gas in intestine. Plasma loss 17 per cent. Plasma gain following release of intestine 21.6 per cent.

Physical Examination showed marked abdominal distention and tympany on percussion. Roentgenograms of the abdomen showed widespread dilatation of loops of small intestine (Fig 3). The plasma volume was 2,116 cc. Satisfactory though not complete decompression was achieved during the following 20 hours by the continuous inhalation of 100 per cent oxygen. This was followed by exploratory celiotomy. A string adhesion running from the mesentery of the ileum to the presacral peritoneum was found completely constricting the ileum. The obstruction was released and an enterostomy performed. After complete deflation on the seventh postoperative day, the plasma volume was 2,832 cc. The loss from distention was therefore only 25.3 per cent, whereas in Case 1, where much less gas seemed to be present the loss was 29.1 per cent.

COMMENT—The varying clinical course of apparently comparable patients with intestinal obstruction similarly treated may well be ascribable to differences in plasma loss due to differences in intra-intestinal pressure which de-

TABLE I
CHANGE IN PLASMA VOLUME, TOTAL BLOOD VOLUME AND HEMATOCRIT, PRODUCED BY INTESTINAL DISTENTION AND DECOMPRESSION

Case No	Date	Pathology	Change in				Hemat-ocrit	N P N Mg %	Urine Sp Gr	24 hrs		Remarks
			Plasma Vol	Red Cell Vol	Total Blood Vol	Plasma Per Cent				Fluid Intake Cc	Urine Output Cc	
1	1/31/40 2/ 1/40 2/ 2/40	Small Bowel Obstruction Distended Decompressed	2,414	-29 6	2,056	4,470	46	25	1 020	4,700	1,250	Postoperative mechanical obstruction treated conservatively Gaseous distention of small intestine shown in X-ray
			3,408	+41 1	2,178	5,580	39		1 018	2,500	1,000	
										3,000	1,000	
2	9/22/39 4 P M 11 30 P M 9/23/39 9/27/39	Small Bowel Obstruction Distended Decompressed Decompressed	2,020*		1,587	3,607	44			350}	700†	Mechanical obstruction due to gallstone in terminal ileum Marked distention of small intestine Mild secondary anemia Gallstone removed at operation, 9/22/39
			1,661	-45 5	1,253	2,914	43			2,900}		
			2,562		1,855	4,417	42			3,600	780	
			3,048	+83 5	1,641	4,689	35	26	1 016	1,910	730	
3	1/ 1/40 1/ 5/40	Small Bowel Obstruction Distended Decompressed	2,494*	-25 3	1,494	4,988	50		1 020	4,200	500	Small bowel obstruction due to right lower quadrant adhesions X-ray of abdomen, 1/1/40 Dilated loops of small bowel in mid- and left epigastrium which show fluid levels N P N 32 mg per cent, 1/2/40 Operative decompression
			3,339	+33 8	2,417	5,756	42		1 018	2,900	1,100	
4	10/18/39 10/19/39 10/24/39	Small Bowel Distention Distended Decompressed	2,531	-40 0	1,685	4,216	40		1 016	2,000	800	Marked distention produced by diet postoperatively, which responded to conservative treatment Moderate secondary anemia
			4,221	+66 7	2,079	6,300	33			2,250	700+	
										2,400	900	

5	Small Bowel Distention	Adynamic ileus; following cystotomy X-ray showed marked gaseous distention of small intestine Responded to nonoperative treatment									
		12/23/39									
		12/24/39	2,868	-23 0	2,034	4,902	41 5	I 022	2,900	500+	
		12/29/39	3,725	+29 9	2,006	5,731	35 0	I 012	4,100	900	
6	Small Bowel Obstruction	Mechanical obstruction due to adherent small intestine in pelvis X-ray, 2/18/40 Many distended loops of small bowel with fluid levels Obstruction released at operation Blood N P N 35 mg per cent, CO ₂ 60 vols per cent, NaCl 380 mg per cent, 2/21/40									
		2/18/40	2,116*	-25 3	2,116	4,232	50	I 026	5,000	300†	
		2/26/40	2,832	+33 8	2,225	5,057	44	I 014	4,700	1,000	
								25			
7	Small Bowel Obstruction	Strangulation obstruction of ileum in femoral hernia, with little or no distention									
		10/10/39									
			2,730*	-17 7	2,520	5,250	48	I 020	1,800	?	
		10/11/39	3,320	+21 6	2,718	6,040	45		3,200	800	
8	Small Bowel Obstruction	History of 3 celiotomies, with evidence of mechanical obstruction Responded promptly to nonoperative therapy On admission, blood CO ₂ 63 vols per cent, N P N 38 mg per cent, chlorides 396 mg per cent									
		12/15/39									
		12/16/39	3,112	-13 3	2,598	5,710	46	I 026	3,400	900	
		12/20/39	3,591	+15 4	2,754	6,345	46	I 002	3,100	700	
9	Large Bowel Obstruction	Obstructive distention of large intestine due to Ca of sigmoid Blood chlorides 502 mg per cent on admission									
		2/ 7/40	2,476*	0	1,754	4,230	41 5	I 020	3,500	500†	
		2/14/40	2,494	0	1,697	4,191	42 0	I 008	4,500	1,300	

* These plasma volume determinations were made on admission, before fluids were administered All other plasma volume determinations were made at least several, and usually 12, hours following the last administration of parenteral fluids

† These figures do not cover a full 24-hour period

depends not only on the volume of incarcerated gas but also on the tone of the intestinal musculature and of the musculature of the abdominal wall

It is nevertheless true, as the following observations will show, that when the volume of incarcerated gas is small or insignificant, the amount of plasma which will be lost in intestinal obstruction is of a relatively low order of magnitude

Case 7—A 74-year-old male entered the hospital with a history of anorexia, nausea, vomiting and constipation during the preceding three days. A tense, painful mass was found in the right inguinal region. A roentgenogram of the abdomen showed only traces of gas (Fig 4) in the intestine. The plasma volume was 2,730 cc. At operation soon



FIG 5—Case 8. Mechanical obstruction of small intestine of 48 hours duration. History of two previous celiotomies. Slight distention. Plasma loss 13 per cent. Plasma gain on decompression 15 per cent.



FIG 6—Case 9. Obstructing carcinoma of sigmoid of one week's duration. Extreme distention of colon. Slight distention of small intestine. No plasma loss.

after admission a strangulated but viable loop of ileum was released from the sac of a femoral hernia which was repaired. On the following day the plasma volume was 3,320 cc. The loss caused by the obstruction was, therefore, only 17 per cent.

COMMENT—The relatively small change in the plasma volume can be explained by the almost complete absence of intestinal distention.

Case 8—A 58-year-old male, with a past history of two celiotomies, one for a perforated duodenal ulcer, and one for appendectomy, complained of intermittent periumbilical pain, nausea, profuse vomiting and constipation for 48 hours before entering the hospital.

Physical Examination showed a severely dehydrated man with a slightly distended abdomen exhibiting visible peristalsis accompanied by periumbilical, colicky pain. Acute tenderness was present over the scar of the appendectomy. The urine showed acetone and a specific gravity of 1.026. The blood nonprotein nitrogen was 38 mg per cent, the

blood chlorides 396 mg per cent and the CO₂ combining power 63 volumes per cent. A roentgenogram of the abdomen showed two or three loops of distended small intestine (Fig 5). The hematocrit was 46, and the plasma volume 3,112 cc. Gastric suction was instituted, and 100 per cent oxygen inhalation administered. Twenty-four hours later, an enema yielded good results and all symptoms and signs of intestinal obstruction disappeared. On the fourth hospital day the hematocrit was still 46, and the plasma volume 3,591 cc—a gain on decompression of only 15.4 per cent.

COMMENT —This is an example of well-developed acute obstruction of the small intestine, in which no marked change in plasma volume occurred in spite of the presence of a considerable degree of dehydration. The slight loss of plasma may be accounted for by the fact that there was comparatively little gas and probably no great increase in pressure in the obstructed bowel. The small volume of gas was presumably due to efficient reverse peristalsis, which may achieve the same desirable decompressive results obtained by duodenal suction.

Case 9 —A 60-year-old woman entered the hospital complaining of severe lower abdominal pain of 24 hours' duration. She gave a history of complete obstipation for one week and repeated nausea and vomiting of 72 hours' duration.

Physical Examination showed marked weight loss, generalized abdominal distention and audible peristalsis. A roentgenogram of the abdomen (Fig 6) showed extreme distention of the right colon and the proximal two-thirds of the transverse colon and a few dilated loops of small intestine. A barium enema showed obstruction in the sigmoid. The plasma volume was 2,476 cc. An immediate cecostomy was performed. The surgeon noted a very tense, enormously distended cecum and soft distention of the distal ileum. Deflation proceeded rapidly thereafter. A week later, when the general physiologic state was in balance, the plasma volume was 2,494 cc, i.e., substantially unchanged.

COMMENT —The failure to observe any fall in plasma volume in this patient in spite of the extreme degree of distention of at least several days' duration is in accord with our experimental finding that distention of the colon *does not* cause a loss in plasma volume such as occurs after small bowel obstruction.

Discussion —It is evident from the foregoing data that a significant loss of plasma occurs in uncomplicated obstruction of the small intestine only when a substantial degree of gaseous distention (Cases 1, 2, 3 and 6) is present. Since a large loss of plasma also occurs in severe distention of functional origin (Cases 4 and 5), the cause of the plasma loss must be attributed to the distention rather than to the obstruction.

The mechanism by which distention causes the plasma loss is, however, uncertain. One of the ideas current in surgical literature is that distention stimulates the accumulation of the excessive volume of fluid commonly present in the bowel in intestinal obstruction. Even if this be true though there is substantial evidence to the contrary,⁸ the dehydration caused by vomiting and transudation into the intestine can be excluded from responsibility for the major part of the plasma loss for the following reasons. In 13 patients subjected to extreme dehydration in a moist, heated cabinet, by Gibson and Kopp,⁹ the plasma loss averaged only 8.7 per cent. The plasma loss in our eight patients with ileus of the small intestine averaged 27.4 per cent. In a normal subject with severe dehydration, Collier and Maddock¹⁰ noted a rise in the nonprotein

nitrogen to 47.5 mg per cent, while the hematocrit increase was only 7.1 per cent. The increase in hematocrit in those of our patients who showed a marked loss of plasma (Cases 1, 2, 3, 4, 5 and 6) was considerably higher, averaging 19.3 per cent, with a range of 12 to 25.5 per cent*. Furthermore, none of these patients, as judged by the data on fluid intake, urinary output and specific gravity, gave evidence of an advanced stage of dehydration comparable to that of Coller and Maddock's subject or of Gibson and Kopp's subjects. In Case 1, for example, in which the obstructive distention caused a plasma loss of 29.6 per cent, the fluid intake and output before and during the obstructive phase was entirely adequate and the blood nonprotein nitrogen was 25 mg per cent, but the hematocrit showed an increase of 15 per cent. This increase in hematocrit must, therefore, have been caused by the loss of plasma which occurred even though the patient was well hydrated. On the other hand, in Case 8, in which dehydration was considerable, indeed, greater than in any of the rest of the group, the plasma loss was only 13 per cent and the hematocrit remained unchanged. *A marked fluctuation in the level of the hematocrit was observed only when marked changes in plasma volume occurred regardless of the amount of dehydration (cf also Cases 1 to 4 and Case 9, Table I).* For these reasons and for others already stated we do not regard fluid deficit responsible for any substantial portion of the plasma loss in obstructive distention. The prevailing idea that the fulminating character of small bowel distention is to be found primarily in the rapid loss of fluid and electrolytes into the bowel lumen and by vomiting, is untenable in view of the above observations and of the well established fact that adequate replacement of this deficiency accomplishes a necessary but not an immediately vital purpose.

Since the plasma loss cannot be accounted for on the basis of fluid and electrolyte imbalance† or on the basis of effects directly referable to the site of obstruction, we are obliged to assume the existence of some other process as yet undiscovered, which is set in motion by the increase in intra-intestinal pressure.

In pursuit of this objective we proceeded experimentally on the basis that the plasma loss in obstruction of the small intestine might at least in part be due to transudation into the tissues caudal to the compressed intra-abdominal veins. This was suggested by the repeated finding in dogs with distention of the small intestine of a greatly increased femoral venous pressure while the jugular venous pressure remained normal. Further, the institution of pneumoperitoneum at pressure levels of 10–20 cm of water (20 cm was used in the small intestine) caused an initial sharp loss of plasma volume, which, however,

* Since the normal hematocrit varies considerably from one person to another, the initial hematocrit reading, which is likely to be made during the stage of distention, is not useful as an index of the extent of plasma loss unless it happens to be considerably above the average normal value. In this case other conditions causing marked red cell volume changes must be excluded.

† It is pertinent in this connection to recall the observations of Taylor, Weld and Harrison,¹¹ who produced very low chloride levels in the blood of dogs without noting any of the other disturbances commonly associated with intestinal obstruction.

was generally not fully sustained. But we could not support this etiologic basis for the loss of circulating plasma because negative results were obtained by plethysmographic studies of the lower extremities and by comparative studies of the wet and dry weights of equal amounts of muscle from the upper and lower extremities. In addition, in several experiments utilizing two feet of small intestine, distention at 20 cm. water pressure, which causes no significant degree of abdominal distention, resulted in an extensive loss of plasma. Finally, contradictory evidence appeared in the observation that dogs with distention of the colon at 35 cm. water pressure, which distends the abdomen quite as much as does distention of the small bowel at 20 cm. of water pressure, did not show a fall in plasma volume, and survived more than twice as long as did those with small bowel distention. We therefore concluded that the plasma loss resulting from distention was not due to the simultaneous expansion of the peritoneal cavity or abdominal wall or to pressure on the intra-abdominal veins.

The failure to observe loss of plasma in distention of the colon in dogs was strikingly confirmed in Case 9, in which no loss of plasma occurred in spite of an extreme degree of obstructive distention of the colon, in which the obstruction was of seven days' duration. It is a possible explanation of the clinical fact that patients with obstructive distention of the colon deteriorate less rapidly than do those with obstructive distention of the small intestine.

The clinical observations, herewith reported, confirm our experimental findings in the following respects: (1) That uncomplicated intestinal obstruction causes a serious fall in the volume of circulating plasma, (2) that this fall in plasma volume occurs even when fluid and electrolyte imbalance is prevented, (3) that the plasma loss is not due to the obstruction itself, but to the distention accompanying it and is generally, but not necessarily, proportional to the degree of distention, (4) that the loss of plasma is probably characteristic of the small, rather than the large, intestine, (5) that the magnitude of the plasma loss in obstructive distention of the small bowel suggests that the loss of plasma is a basic process in the fatal effects of uncomplicated obstruction of the small intestine.

The inference is clear that the therapy of intestinal obstruction must take cognizance of this important factor in the pathologic physiology of the disease, for even when effective decompression is achieved, the effort may fail unless the plasma deficiency is corrected in time to prevent irreversible changes.

CONCLUSIONS

(1) Patients with distention of the small intestine, whether of functional or mechanical origin, show a considerable loss in the volume of circulating plasma.

(2) As the plasma volume falls the hematocrit rises. This increase in hematocrit is far greater than can be explained by dehydration, however severe.

(3) Dehydration and electrolyte imbalance are not responsible for the greater part of this plasma loss

(4) Effective decompression of the small intestine restores the plasma volume toward normal

(5) The extent of the plasma loss is generally, but not necessarily, proportional to the degree of gaseous distention as estimated roentgenologically and by physical examination

(6) In a patient with a marked obstructive distention of the colon no loss of plasma occurred

REFERENCES

- ¹ Gendel, S., and Fine, J. The Effect of Acute Intestinal Obstruction on the Blood and Plasma Volumes. *ANNALS OF SURGERY*, 110, 25, 1939
- Fine, J., Rosenfeld, L., and Gendel, S. The Role of the Nervous System in Acute Intestinal Obstruction. *ANNALS OF SURGERY*, 110, 411, 1939
- ² Fine, J., and Gendel, S. Plasma Transfusion in Experimental Intestinal Obstruction. *ANNALS OF SURGERY*, 112, 240, 1940
- ³ Fine, J., Fuchs, F., and Gendel, S. Changes in Plasma Volume Due to Decompression of the Distended Small Intestine. *Arch Surg*, 40, 710, 1940
- ⁴ Fine, J., Fuchs, F., and Mark, J. The Effect of Desoxycorticosterone on the Plasma Volume in Acute Intestinal Obstruction. *Proc Soc Exper Biol and Med*, 43, 514-516, 1940
- ⁵ Unpublished data
- ⁶ Gibson, J. G., and Evelyn, K. A. Clinical Studies of the Blood Volume. *Jour Clin Invest*, 17, 153, 1938
- ⁷ Gatch, W. D., and Culbertson, C. G. Circulation Disturbances Caused by Intestinal Obstruction. *ANNALS OF SURGERY*, 102, 619, 1935
- ⁸ Gibson, J. G., and Kopp, I. Studies in the Physiology of Artificial Fever. I. Changes in the Blood Volume and Water Balance. *Jour Clin Invest*, 17, 219, 1938
- ⁹ Collier, F. A., and Maddock, W. G. A Study of Dehydration in Humans. *ANNALS OF SURGERY*, 102, 947, 1935
- ¹⁰ Taylor, N. B., Weld, C. B., and Harrison, G. K. Experimental Intestinal Obstruction. *Jour Canad Med Assn*, 29, 227, 1933

PLASMA LOSS IN SEVERE DEHYDRATION, SHOCK AND OTHER CONDITIONS AS AFFECTED BY THERAPY*

A S MINOT, PH D, AND ALFRED BLALOCK, M D

NASHVILLE, TENN

FROM THE DEPARTMENTS OF PEDIATRICS AND SURGERY, VANDERBILT UNIVERSITY, NASHVILLE, TENN

SHOCK may be defined as peripheral circulatory failure resulting from a discrepancy in the size of the vascular bed and the volume of intravascular fluid. In primary or neurogenic shock vasodilatation or increase in the vascular bed is the most important initial change. In secondary or hematogenic shock, a decrease in the volume of circulating blood plays a primary rôle. Frequently, in clinical conditions the two factors of vasodilatation and loss of circulating volume work together to cause failure of the circulation. In this discussion we shall consider mainly the factors which lead to a deficiency of intravascular fluid and therapeutic methods of preventing and treating secondary or hematogenic shock.

Under *normal conditions* many factors cooperate to maintain a normal amount of fluid in the body and a normal partition of this total water in the tissue cells, the extracellular spaces and in the vascular system. The intake of water and electrolyte must keep pace with the loss of these elements from the body. There must be sufficient plasma protein to attract and hold an adequate volume of fluid in the blood stream. There is the selective permeability of the capillaries which allows water and crystalloids to pass freely but withholds most of the protein in the blood stream. There is kidney activity which removes metabolic waste products and any excess of fluid or electrolytes taken into the body. Numerous other factors might also be mentioned. A sufficiently serious abnormality in any of these factors may result in disastrous changes in the amount and partition of body fluid.

We are particularly interested, here, in *abnormal conditions* which may lead to a serious reduction in the volume of circulating blood. Among the simpler conditions which lead most obviously to such a reduction are *severe dehydration* and *extensive hemorrhage*. When replacement of water and electrolytes fails to keep pace with an excessive loss such as occurs, for example in severe diarrhea there is a marked reduction in body water. Since the loss is mainly one of water and salts both the plasma proteins and cellular elements of the blood become more concentrated. With the rise in plasma protein, more and more of the reserve of extracellular water is drawn into the blood stream to replace the loss which has occurred. Thus in simple dehydration of this type it is not until the readily available extracellular reserve of water has been largely depleted that a serious reduction of blood

* Aided by a Grant from the Division of Medical Sciences of the Rockefeller Foundation

Read before the American Surgical Association St. Louis, Mo. May 1, 2, 3 1940

volume occurs. One needs, however, only to recall the familiar picture of circulatory collapse which is seen in infants with severe watery diarrhea to realize that a point is eventually reached in simple dehydration when the reduced volume of thick, viscous blood becomes inadequate to maintain the peripheral circulation. Massive loss of whole blood through hemorrhage results in a dilution rather than a concentration of protein and cellular elements but rather promptly reduces the blood volume to an amount incompatible with sustained circulation. This condition is a simple one unless prolonged reduction in volume leads to secondary changes, to be discussed later, which lead to the inability to retain fluid restored to the blood stream.

In addition to these simpler types of loss of fluid, there are a variety of conditions which cause a reduction of the circulating blood volume through an excessive transfer of plasma elements from the blood stream into the extracellular spaces. Such an abnormal partition of body water may arise simply from a *nutritional lack* of adequate plasma protein. This is the type of disturbance that occurs in nutritional edema. Weech, Snelling and Goettsch¹ found that there is a progressive loss of fluid from the blood vessels as the plasma proteins are reduced, resulting first in a latent and subsequently in an evident edema. Jones and Eaton² observed that edema may occur as a complication of a variety of surgical conditions and operations and that it is exaggerated if large quantities of normal salt solution are administered. It had been noted previously, by Smith and Mendel,³ that the intravenous injection of large quantities of solutions of various neutral salts results in edema if hypoproteinemia exists, whereas otherwise edema does not occur. Thus there is present in hypoproteinemia a reduction in ability to attract and hold fluid in the blood stream, and an escape and accumulation of pathologic amounts of fluid in the tissue spaces occurs.

Hypoproteinemia on a nutritional basis does not often lead to serious circulatory failure, but its correction is of importance because of the likelihood of the development of postoperative complications. It is likely that this abnormality is responsible for some instances of pulmonary edema and pneumonia. There is a retardation in the healing of incisions⁴ and an increase in the incidence of disruption of wounds.⁵ Mecray, Barden and Ravdin⁶ found that the edema associated with hypoproteinemia may prevent the patency of recent intestinal anastomoses.

Frequently, a similar and more serious abnormal partition in body water occurs not because of a primary deficiency in plasma protein but because the *capillaries have been injured* to the point of letting plasma protein as well as water and crystalloids pass through the capillary endothelium into the tissue spaces. Mechanical, chemical or thermal trauma and oxygen lack are common causes of increased permeability of the capillaries. Underhill and Fisk⁷ found that the fluid which escapes at the site of a burn is almost identical with blood serum in its composition. Beard and Blalock⁸ found that the protein content of fluid which is lost as a result of burns, of mild trauma to an extremity and to the intestines is the same as that of the blood plasma.

PLASMA LOSS

Clinically, one sees such injury initiated by mechanical trauma, burns to the skin, inflammatory processes, distention of the intestines with resultant interference with the circulation, *etc*. Whatever the initiating cause may be, the transfer of plasma leading to circulatory impairment is similar. Even in instances in which a prolonged decline in the blood pressure and blood volume is caused by uncomplicated hemorrhage,⁹ a marked increase in capillary permeability occurs and plasma is lost.

TABLE I

CHANGES DURING THE DEVELOPMENT OF CIRCULATORY FAILURE FOLLOWING A BURN

Dog Anesthetized with Sodium Barbital

Time	Plasma Volume Cc	Concen- tration Plasma Protein Per Cent	Total Circu- lating Protein Gm	Hemato- crit Percent- age Cells	Blood Pressure Mm Hg	Loss in Per Cent	
						Plasma Volume	Total Circu- lating Protein
Preliminary	523	7.03	36.6	53.4	135		
4 hrs after burn				59.5	130		
6 hrs after burn	347	6.78	23.5	62.0	114	32.6	35.8
13 hrs after burn	318	6.44	20.5	66.3	76	39.0	44.0
14 hrs after burn				68.0	45		
15 hrs after burn					Died		

The alterations that occur in burns are illustrated by the experimental results presented in Table I. This anesthetized animal developed peripheral circulatory failure several hours after receiving an extensive burn. No supportive treatment of any kind was given. Measurements of blood and plasma volumes, hematocrit, plasma protein concentration and blood pressure were made before and at intervals after the burn was inflicted. The total circulating protein was calculated by multiplying the plasma volume by the concentration of protein. Approximately 32 per cent of the original plasma volume had been lost by the end of the first six hours. Coincident with the loss of plasma, there was a rise in the percentage of cells per unit volume of blood. The concentration of protein did not increase with that of the cellular elements as would be the case if only fluid and electrolytes had been lost. On the contrary, there was a slight decrease in the plasma protein concentration, and on calculating the total circulating protein, it was found that there had been a loss of about 35 per cent of the original amount during the first six hours. As always occurs, the burned area became swollen and edematous. Analysis of the fluid which accumulated in the subcutaneous tissues revealed a protein content approaching that of plasma. In spite of the large local loss of plasma fluid, electrolytes and protein and the associated

reduction in blood volume, the blood pressure at the end of six hours was essentially the same as during the control period. The pressure was doubtless maintained by virtue of general vasoconstriction which is known to occur in the hematogenic type of shock. With the passage of time, the changes observed during the first six hours progressed. There was an increase in the hemoconcentration and the plasma loss continued until only 61 per cent of the original volume remained while the total circulating protein was reduced to 56 per cent of the initial amount. It was not until a few hours before death that the blood pressure began to decline significantly and from this point on fatal circulatory failure progressed rather rapidly.

Scudder and his associates^{10, 11} have investigated, very extensively, the alterations in blood potassium in various conditions. They found marked increases in plasma potassium in severe dehydration, following burns, and in other types of injury. They suggest that potassium is an ever present H-substance which may be the responsible agent in the causation of shock. On the other hand, their hypothesis is not supported by the findings of Bisgaard, McIntyre and Osheoff¹² and Greenwood, Haist and Taylor¹³. It is quite possible that an elevation of plasma potassium may impair further the already handicapped circulation. Also, in the terminal stages of shock there is a more or less serious reduction of alkali reserve, largely due to the accumulation of lactic acid and other acid metabolites as the circulation and oxygenation fail.

Although details of the total picture vary somewhat with the nature of the condition which has initiated the injury, observations such as we have just described are characteristic of hematogenic shock in general and demonstrate how rapidly an increase in the permeability of capillaries leads to disastrous circulatory changes. In the presence of an injury which allows an extensive and progressive loss of circulating protein as well as fluid, there is a reduction in the colloidal osmotic pressure of the remaining blood and hence an inability to draw effectively on extravascular reserves of fluid to replenish the volume lost from the blood stream. Consequently, a much more serious reduction in blood volume results from a loss of plasma than would be caused by a considerably more extensive loss of fluid and crystalloids. In instances of localized trauma the loss of plasma is at first mainly into the injured area. Later the loss becomes more general as the previously uninjured capillary beds become more permeable as a result of oxygen lack imposed by reduced circulating volume and prolonged compensatory vasoconstriction¹⁴. Similarly, a condition which at the start involves no capillary injury but only simple dehydration may lead secondarily to vascular changes which cause a loss of plasma protein. In any case, the combined handicaps of reduced volume, increased permeability and the deleterious effects of electrolyte change bring about a rapid failure of the circulation.

Prevention and Treatment—The problem in the treatment of impending hematogenic shock is to restore and maintain a more effective circulation in the presence of the abnormalities such as we have observed in the untreated

subject Steps must be taken to overcome the discrepancy between the circulating volume and the size of the vascular bed Attempts to increase *vasoconstriction* with such *drugs* as adrenalin, pituitrin, ephedrine, *etc*, have met with failure as a means of preventing shock Prolonged vasoconstriction is one of the characteristics of untreated hematogenic shock and, while it is a valuable temporary compensatory mechanism, it later becomes a factor¹⁴ which contributes to further loss of plasma It is not surprising, therefore, that the net result of these constrictor drugs is to contribute to this secondary vicious cycle of events

Considerably more promising, according to recent reports, are the results obtained from the administration of *cortical extract* From the experimental viewpoint, Heuer and Andrus¹⁵ found that cortical extract is of value in preventing shock and of less value in treating it Peila and his associates¹⁶ stated that the parenteral administration of salt solution combined with cortical hormone is more effective than either alone in the prevention and treatment of histamine shock in rats and mice Fine, Fuchs and Mark¹⁷ found that the marked fall in plasma volume in dogs subjected to continuous distention of the small intestine is at least partly prevented by the intravenous administration of desoxycorticosterone, but there was no prolongation of the life of the animals Somewhat encouraging results in the treatment of patients have been reported by Hartman,¹⁸ Wilson, Rowley and Gray,¹⁹ Wohl, Buins and Pfeiffer,²⁰ Reed,²¹ Scudder,¹¹ and by others At our present state of knowledge, it is impossible to understand through what mechanisms this agent exerts its favorable influence on the maintenance of a more effective intravascular volume Possibly much of its influence may be related to its effect in restoring the distorted sodium-potassium ratio in the blood and body fluids However useful an adjunct cortical extract may prove to be, a large part of treatment must still be replacement of the elements which have been lost from the blood stream

The difficulty encountered in *fluid replacement therapy* varies greatly in different conditions No uniform plan of treatment could be outlined which would be equally successful for a group of patients Rather, the physiologic needs and the pathologic handicaps of each individual patient have to be considered and evaluated and the treatment employed regulated accordingly If the problem is merely to restore fluid and electrolytes to an acutely dehydrated patient with a normal amount of plasma protein and with uninjured capillaries, treatment is relatively simple On the other hand, the restitution and maintenance of an effective circulating volume of blood in a patient whose capillaries have allowed and are continuing to allow a loss of all the plasma elements including protein is far more difficult

In any case, the patient's needs for fluid and electrolytes must be met We will first consider the effect of the administration of solutions of crystalloids, *ie*, glucose and salts to patients whose blood volume has been depleted in various ways A fundamental principle in the restitution of fluid is that if both water and salts have been lost in the process of dehydration, both water and salts must be restored Water cannot be retained in the body without

sufficient salts to make an isotonic solution. Any attempt to restore water alone in the presence of a salt deficiency leads to physiologic disturbances, as for example, the "heat cramps" experienced by workmen who have lost salt and water through excessive sweating and then attempt to overcome dehydration by drinking water alone. Glucose solutions, valuable as they may be as a source of nutrition, are equivalent to water alone, as far as fluid and electrolyte equilibrium is concerned, and hence cannot overcome dehydration when salts have been lost. Solutions of salts *must* be employed for this purpose. Since sodium is the chief cation which is lost from the body, sodium salts are replaced. Isotonic solutions of sodium chloride are most commonly employed but a recognition of both the quality and quantity of electrolyte loss influences the solution chosen for restitution therapy. If there has been a large loss of chloride ion, as in persistent vomiting, sodium chloride is the salt indicated. If, on the other hand, there has been a marked depletion of the alkali reserve, the administration of sodium bicarbonate or sodium lactate, which will yield bicarbonate, will more promptly restore normal electrolyte equilibrium. Methods for determining the quantity and composition of the repair solutions that are needed have been described by Maddock and Collier²².

If the salt loss has been excessive and if there is an alarming distortion in the potassium-sodium relationship, the more rapid administration of sodium salts in hypertonic solutions is indicated. As a general thing, however, isotonic solutions are less disturbing to the patient.

The *route of administration* of such solutions is another problem which should receive individual consideration according to the needs and handicaps of the patient. Will fluid be retained when given by mouth, will fluid be absorbed from the gastro-intestinal tract if given orally or by proctoclysis, will fluid be absorbed when given subcutaneously, and what disposition will be made of fluid that is given intravenously? Any of these routes is satisfactory for the simple restoration of water and electrolytes to overcome dehydration. Frequently vomiting or diarrhea or infection or an operation makes the gastro-intestinal route impractical, but good results may be obtained when fluid and electrolytes are supplied in suitable amounts either by the subcutaneous or intravenous routes.

In the patient with a primary nutritional lack of plasma protein or in one who has lost plasma protein as well as fluid through injured capillaries, the problem is more difficult. Such patients absorb fluids poorly from the gastro-intestinal tract. Fluid given subcutaneously also tends to remain unabsorbed in the tissues where it is placed. It is easy to see why this is true. Most of the difficulty in patients of this type arises before treatment is started from a transfer of plasma elements from the blood to the tissues due to an inability to attract and hold water in the blood stream. The same handicap which made it impossible for the patient to maintain a normal partition of body water before treatment makes it impossible for him to absorb and maintain in the blood stream fluid which is administered into the tissue spaces. This leaves only the intravenous route as an effective means of introducing fluid

There is no doubt but that the intravascular volume can be temporarily increased by the direct introduction of salt solutions into the vascular system. The prompt temporary response of most patients with depleted blood volume to such treatment is well known. It is equally well known that this favorable response is often disappointingly transient and the blood stream again becomes dehydrated and the circulatory impairment progresses in spite of the continued introduction of fluid.

A study^{23, 24, 25} of what occurs when aqueous solutions are given intravenously to experimental animals or patients with *increased capillary permeability* explains the reason for the failure of this form of therapy. The introduction of aqueous solutions dilutes the plasma colloids in the blood stream. If they are already low, further dilution brings them to a concentration which makes it impossible to hold the administered fluid in the blood stream. Tissue edema develops while the blood stream remains dehydrated. If there is extensive capillary damage so that protein escapes with fluid, the continuous administration of fluid by vein washes out more protein and as a result may actually reduce rather than increase the volume of circulating blood.

The best guide as to the disposal being made of fluid administered by vein is afforded by frequent measurements of hematocrit or hemoglobin and of plasma protein. If fluid is being retained in the blood stream, both hemoglobin and plasma protein should decrease in concentration together. When, as so often happens, the paradoxical observation is made that the concentration of protein is decreasing while that of hemoglobin is increasing as fluids are given intravenously, it can only mean that plasma is being lost from the blood stream and that the treatment is accomplishing nothing toward restoring a more effective circulating volume. Under these circumstances, colloid as well as aqueous solutions must be administered before fluid can be retained in the blood stream. It is too well recognized to require further emphasis here that transfusions of blood or plasma should be given early in the supportive treatment of impending hematogenic shock when there has been protein loss. A point which may need further emphasis, however, is the really enormous amount of colloid which may be required and which will ultimately bring about successful results in patients with extensive capillary injury. One can calculate, more or less accurately, the amount of fluid and electrolyte a person needs to replace what has been lost and to keep pace with his continuous needs. There is no such definite approach to the amount of colloid required if its loss through damaged capillaries is continuous. The rate of plasma loss can be cut down somewhat by conservatism in the amount of aqueous fluid given by vein. In this connection, it may be advantageous at times to give aqueous solutions that are hypertonic rather than isotonic because the higher salt content temporarily attracts and holds more fluid in the blood stream.

In Table II are collected observations made upon two anesthetized dogs receiving continuous mild intestinal trauma. One was given a continuous

slow intravenous injection of 0.9 per cent sodium chloride solution throughout the experiment. The other received a continuous slow transfusion of blood serum. In spite of the continued administration of saline there was a progressive decrease in plasma volume and an increase in the concentration of cellular elements. During the same period there was a gradual decrease in the concentration of plasma protein and a loss of well over half the total circulating protein during a period of seven hours. In the dog receiving serum, there was a moderate increase in plasma volume and total circulating

TABLE II

COMPARISON OF EFFECT OF CONTINUOUS INTRAVENOUS INJECTION OF NORMAL SALINE AND OF BLOOD SERUM IN DOGS RECEIVING CONTINUOUS INTESTINAL TRAUMA

Fluid Employed	Time from Start	Amount of Fluid Administered Cc	Concentration Plasma Protein Per Cent	Plasma Volume Cc	Total Circulating Protein Gm	Hematocrit Per Cent Cells
0.9 per cent saline	Control	0	6.2	942	58.6	52.4
	1° 30'	297	5.7	835	48.3	56.3
	3° 30'	693	5.1	865	44.1	54.5
	5° 30'	1,089	4.3	650	28.1	61.7
	7°	1,388	3.3	672	22.2	60.7
Blood serum	Control	0	5.0	474	24.0	42.2
	1° 30'	123	5.1	578	29.7	38.0
	3° 30'	280	5.4	572	31.1	37.8
	5° 30'	444	5.9	546	32.7	40.0

protein with little change in hematocrit. Assuming that the serum administered contained 5-6 per cent protein, it is evident that an amount of protein equivalent to the total plasma protein present before the initiation of capillary injury was given during five and one-half hours. The continued loss from the blood stream is shown by the fact that this large replacement caused only a moderate increase in the total circulating protein.

We know of no specific means of directly influencing the increased permeability of injured capillaries unless cortical extract proves to be an agent which can accomplish this. Our approach has to be rather an attempt to give colloid fast enough to increase the level in the blood to the point of retaining an effective circulating volume in spite of the losses that may occur. To do this often requires transfusions far in excess of what would ordinarily be considered adequate. This is illustrated by a recent experience in the Vanderbilt Hospital in the treatment of an adult with burns of almost one-half of the body surface. During the first 19 days that the patient was in the hospital the total quantity of fluids that were given intravenously consisted of 5,000 cc of blood plasma, 2,650 cc of whole blood, and 8,700 cc of salt or glucose solutions. The greatest quantity of salt or glucose solution given intravenously in any one 24 hour period was 1,500 cc. Fluids were administered by other routes in larger amounts. Even though large quantities of colloidal solutions were given, and the intravenous injections of solutions of crystalloids were

somewhat restricted, the total serum proteins on several occasions fell to less than 4 Gm per 100 cc. This illustrates the really tremendous amounts of blood and plasma which are required to maintain a fairly satisfactory level of plasma protein and an effective volume of circulating blood. It is believed that the patient's recovery was due to the administration of large quantities of colloidal solutions. The local therapy of the burn consisted only of the application of compresses of Dakin's solution. The experience of Gatch²⁶ and of Trusler, Egbert and Williams²⁷ is similar to that which we have related.

Transfusion of *blood plasma* is probably the method of choice for restoration of plasma volume. The use of plasma rather than whole blood avoids further burdening of the circulation with cellular elements which are already present in high concentration. Volume for volume, plasma transfusions introduce protein approximately twice as fast as when whole blood is given. There is less danger of reactions from plasma than from any of the more artificial preparations which have been suggested. The disadvantages of plasma are the additional technical difficulties and time required for preparing plasma for transfusions and the larger amounts of blood which must be furnished by donors. Even in instances in which the primary disturbance is the loss of whole blood, Levinson, Neuwelt and Necheles²⁸ and others have found that the introduction of blood plasma or serum exerts markedly beneficial effects. The value and convenience of having available a "Plasma Bank" can hardly be overestimated in the treatment of patients with capillary injury. Here, a delay of a few hours may preclude the possibility of a favorable response. Without a "Bank" it is impossible to procure plasma without considerable delay. Lacking plasma, transfusions of whole blood should be administered promptly and repeatedly.

The consensus of opinion appears to have been that there is little choice between blood serum and blood plasma and that there is little danger of reactions with either of these. In recent publications, Strumia, Wagner and Monaghan^{29, 30} state that blood serum is much more apt to cause unfavorable reactions than is plasma, and that the difference is brought about by the process of fibrin precipitation. This work has not as yet been confirmed.

Many attractions are offered by desiccated or *lyophilized blood serum*. The dried powder can be kept indefinitely. It can be dissolved in a smaller volume of water than that of the original plasma and so a solution richer in protein than fresh plasma can be introduced. The chief disadvantages are the cost and difficulty of preparing the dried serum and the frequency of reactions following the injection of the redissolved powder. Ravdin³¹ is of the opinion that the frequency of reactions is such that lyophilized serum should not be used. Strumia, Wagner and Monaghan^{29, 30} state that the reactions which have been observed following the intravenous administration of lyophilized serum are due not to a change induced by the process of desiccation but to the use of serum. It is further stated that lyophilized or cryochem plasma causes no reactions.

Acacia solutions have been employed to some extent as a means of introducing colloid. Acacia is not a protein but it has the property, similar to

that of plasma protein, of attracting and holding water in the blood stream. As an emergency measure, when whole blood or plasma cannot be procured for transfusion, much can be accomplished in restoring the blood volume by intravenous injections of acacia. The frequency of reactions to such injections and the prolonged storage of acacia in the liver and other tissues make its use inadvisable except in emergencies. Experimental work indicates that the use of *ascitic fluid* may, at some time, become a practical means of supplementing the plasma volume. The protein content of ascitic fluid is somewhat less than half of that of blood plasma.

CONCLUSIONS

Failure of the peripheral circulation due to an inadequate volume of circulating blood may result from severe dehydration, extensive hemorrhage, and from conditions which allow a transfer of plasma elements from the blood stream into the tissue spaces. The aim of supportive treatment in impending shock of this type is to restore and maintain a more adequate volume of intravascular fluid. The character and amount of fluid employed for replacement therapy as well as the route of administration must be adapted to the requirements and handicaps of the individual patient. In the absence of capillary injury, the restitution of whole blood after hemorrhage or the replacement of fluid and electrolytes in dehydration is a relatively simple problem. In patients in a poor state of nutrition or in whom there is either localized or general injury to capillaries, it is much more difficult to maintain the proper distribution of administered fluids. The intravenous administration of solutions of crystalloids to such patients often leads to the production of massive edema while the blood stream remains dehydrated or even becomes further decreased in volume. Under these conditions the administration of liberal amounts of plasma colloid is an indispensable factor in the restoration of fluid and electrolyte equilibrium.

BIBLIOGRAPHY

- ¹ Weech, A. A., Snelling, C. E., and Goettsch, E. Relation Between Plasma Protein Content, Plasma Specific Gravity and Edema in Dogs Maintained on Protein Inadequate Diet and in Dogs Rendered Edematous by Plasmapheresis. *Jour Clin Invest*, 12, 193, 1933.
- ² Jones, C. M., and Eaton, F. B. Postoperative Nutritional Edema. *Arch Surg*, 27, 159, 1933.
- ³ Smith, A. H., and Mendel, L. B. The Adjustment of Blood Volume After Injection of Isotonic Solutions of Varied Composition. *Am Jour Physiol*, 53, 323, 1920.
- ⁴ Harvey, S. C., and Howes, E. L. Effect of High Protein Diet on Velocity of Growth of Fibroblasts in Healing Wound. *ANNALS OF SURGERY*, 91, 641, 1930.
- ⁵ Thompson, W. D., Ravdin, I. S., and Frank, I. L. Effect of Hypoproteinemia on Wound Disruption. *Arch Surg*, 36, 500, 1938.
- ⁶ Mecray, P. M., Jr., Barden, R. P., and Ravdin, I. S. Nutritional Edema. Its Effect on Gastric Emptying Time Before and After Gastric Operations. *Surgery*, 1, 53, 1937.
- ⁷ Underhill, F. P., and Fisk, M. E. Studies on Mechanism of Water Exchange in Animal Organism. Composition of Edema Fluid Resulting from Superficial Burn. *Am Jour Physiol*, 95, 330, 1930.

- ⁸ Beard, J W, and Blalock, A Experimental Shock Composition of Fluid That Escapes from Blood Stream after Mild Trauma to Extremity, after Trauma to Intestines and after Burns Arch Surg, 22, 617, 1931
- ⁹ Blalock, A Shock Further Studies with Particular Reference to Effects of Hemorrhage Arch Surg, 29, 837, 1934
- ¹⁰ Scudder, J, Smith, M E, and Drew, C R Plasma Potassium Content of Cardiac Blood at Death Am Jour Physiol, 126, 337, 1939
- ¹¹ Scudder, J Shock Blood Studies as a Guide to Therapy Philadelphia, J B Lippincott Co, 1940
- ¹² Bisgard, J D, McIntyre, A R, and Osherooff, W Studies of Sodium, Potassium and Chlorides of Blood Serum in Experimental Traumatic Shock, Shock of Induced Hyperpyrexia, High Intestinal Obstruction and Duodenal Fistulas Surgery, 4, 528, 1938
- ¹³ Greenwood, W F, Haist, R E, and Taylor, N B The Plasma Potassium Following Intestinal Obstruction in Dogs Surgery, 7, 280, 1940
- ¹⁴ Freeman, N E Decrease in Blood Volume After Prolonged Hyperactivity of Sympathetic Nervous System Am Jour Physiol, 103, 185, 1933
- ¹⁵ Heuer, G J, and Andrus, W deW Effect of Adrenal Cortical Extract in Controlling Shock Following Injection of Aqueous Extracts of Closed Intestinal Loops ANNALS OF SURGERY, 100, 734, 1934
- ¹⁶ Perla, D, Freiman, D G, Sandberg, M, and Greenberg, S S Prevention of Histamine and Surgical Shock by Cortical Hormone (Desoxycorticosterone Acetate and Cortin) and Saline Proc Soc Exper Biol and Med, 43, 397, 1940
- ¹⁷ Fine, J, Fuchs, F, and Mark, J Effect of Desoxycorticosterone on Plasma Volume in Intestinal Obstruction Proc Soc Exper Biol and Med, 43, 514, 1940
- ¹⁸ Hartman, F A Studies on Function and Clinical Use of Cortin Ann Int Med, 7, 6, 1933
- ¹⁹ Wilson, W C, Rowley, G D, and Gray, N A Acute Toxemia of Burns Effect of Suprarenal Cortex in Treatment Lancet, 1, 1400, 1936
- ²⁰ Wohl, M G, Burns, J C, and Pfeiffer, G High Intestinal Obstruction in Dog Treated with Extract of Adrenal Cortex Proc Soc Exper Biol and Med, 36, 549, 1937
- ²¹ Reed, F R Acute Adrenal Cortex Exhaustion and Its Relationship to Shock Am Jour Surg, 40, 514, 1938
- ²² Maddock, W G, and Collier, F A Water Balance in Surgery J A M A, 108, 1, 1937
- ²³ Beard, J W, Blalock, A *et al* Intravenous Injections Jour Clin Invest, 11, 249-325, 1932
- ²⁴ Minot, A S Factors Influencing the Disposition of Fluids Given Intravenously Am Jour Dis Child, 54, 185, 1937 (Transactions)
- ²⁵ Minot, A S, and Dodd, K Jour Pediat, in press
- ²⁶ Gatch, W D Personal communication, 1939
- ²⁷ Trusler, H M, Egbert, H L, and Williams, H S Burn Shock The Question of Water Intoxication as a Complicating Factor Blood Chemical Studies and Report of Extensive Burn Treated by Repeated Transfusions of Blood and Blood Plasma J A M A, 113, 2207, 1939
- ²⁸ Levinson, S O, Neuwelt, F, and Necheles, H Human Serum as a Blood Substitute in the Treatment of Hemorrhage and Shock J A M A, 114, 455, 1940
- ²⁹ Strumia, M M, Wagner, J A, and Monaghan, J F The Use of Citrated Plasma in the Treatment of Secondary Shock J A M A, 114, 1337, 1940
- ³⁰ Strumia, M M, Wagner, J A, and Monaghan, J F The Intravenous Use of Serum and Plasma, Fresh and Preserved ANNALS OF SURGERY, 111, 623, 1940
- ³¹ Ravdin, I S Some Recent Advances in Surgical Therapeutics ANNALS OF SURGERY, 109, 321, 1939

PHYSIOLOGIC FACTORS REGULATING THE LEVEL OF THE PLASMA PROTHROMBIN *

JONATHAN E RHOADS, M D

PHILADELPHIA, PA

FROM THE HARRISON DEPARTMENT OF SURGICAL RESEARCH SCHOOLS OF MEDICINE UNIVERSITY OF PENNSYLVANIA AND THE HOSPITAL AND THE GRADUATE HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA PHILADELPHIA, PA

THE PROTHROMBIN CONCENTRATION of the blood became important in the management of surgical patients as the result of the demonstration by Quick, Stanley-Brown and Bancroft¹ that hypoprothrombinemia was at times associated with obstructive jaundice. However, it was not until Warner Smith and Brinkhous² demonstrated that the prothrombin level in these patients could be restored to normal by the administration of vitamin K and bile salts, that a widespread interest developed in the prothrombin level of the jaundiced patient.

The hypothesis upon which this treatment was based was that vitamin K was necessary for prothrombin formation and that bile salts were necessary for its absorption from the bowel. When the common duct is obstructed, so that bile is prevented from reaching the intestine, vitamin K is not absorbed into the portal circulation, and prothrombin formation stops as soon as the stores of vitamin K are exhausted. Quick,³ who first proposed this hypothesis, was also the first to encounter a patient that disproved it.⁴ The patient in question had a prothrombin level which at one time was as low as 2.5 per cent and failed to respond to a vitamin K substrate, so that it was necessary to resort to transfusions to check hemorrhage.

Various authors have reported varying degrees of success in treating hypoprothrombinemia with vitamin K substrates. During 1938 and the first half of 1939, Cerophyl was employed in treating the cases of hypoprothrombinemia studied in the Harrison Department of Surgical Research at the University of Pennsylvania. The prothrombin time returned to normal in 69 per cent of the cases treated and showed an improvement in an additional 13 per cent. Three cases, or 18 per cent, however, failed to show any improvement. Following the isolation⁵ and synthesis of vitamin K₁ by Doisy and his associates, a number of synthetic substances with vitamin K activity became available for clinical use. One of these, 2-methyl-1, 4-naphthoquinone proved to be even more active than naturally occurring K₁ extracted from alfalfa. It was hoped that this substance, powerful as it was, would cause a favorable rise in the prothrombin level of those patients that had failed to respond satisfactorily to vitamin K substrates. The results obtained are shown in Table I. In 73 per cent the prothrombin level returned to normal, in an additional 9 per cent it improved, but in 18 per cent there was no improvement. It is probable, therefore, that the solution of this problem does not lie in the direction of the administration of more active preparations.

* Read before the American Surgical Association, St. Louis, Mo., May 1, 2, 3, 1940.

having a K activity Experience with four other synthetic preparations, one of which was given intravenously, has so far confirmed this impression It should be stated, however, that the more potent preparations achieve a much prompter response in those patients that do respond favorably than was the case when vitamin K substrates were used

TABLE I

A COMPARISON OF THERAPEUTIC RESULTS IN THE TREATMENT OF HYPOPROTHROMBINEMIA WITH CEROPHYL (VITAMIN K SUBSTRATE) AND 2-METHYL-1, 4-NAPHTHOQUINONE

	Patients Treated	Prothrombin Returned to Normal		Partial Improvement		No Improvement	
		No	Per Cent	No	Per Cent	No	Per Cent
Cerophyl	16	11	69	2	13	3	18
2-methyl-1, 4-naphthoquinone	22	16	73	2	9	4	18

In general, it has been found that hypoprothrombinemia in patients with common duct obstruction due to cholelithiasis responds well, but that hypoprothrombinemia in patients with cirrhosis as a rule responds very poorly Clinical evidence, therefore, points to hepatic cellular injury as the major cause of the failure to obtain a satisfactory response following adequate therapy Vitamin K deprivation may explain the clinical hypoprothrombinemia seen in hemorrhagic disease of the newborn

Some of the experimental evidence bearing upon this mechanism has been confusing as any factor capable of producing liver damage may also be capable of inhibiting bile salt formation The principal experimental methods of inducing a fall in the plasma prothrombin level are summarized in Table II

TABLE II

EXPERIMENTAL METHODS OF PRODUCING HYPOPROTHROMBINEMIA

Method	Animal	Approximate Time Required
Vitamin K-free diet	Chick	1 to 3 wks
	Rat	
Biliary fistula	Dog	2 to 4 mos
	Rat	3 to 4 wks
Ligation of common bile duct	Rat	Not stated
Chloroform anesthesia	Dog	<24 hrs
Carbon tetrachloride	Dog	<24 hrs
Phosphorus	Dog	Not stated
Spoiled sweet clover hay	Rabbits	2 to 3 days
	Cattle	
Partial hepatectomy	Rat	<24 hrs
Total hepatectomy	Dog	Progressive decline evident within 1 to 4 hrs
Liver trauma	Dog	2 hrs

The bile fistula methods of producing hypoprotrombinemia are relatively slow—two dogs in our laboratory failed to show a significant fall in over 15 weeks. Contrasted with this is the rapid drop in the same species induced by the administration of chloroform or carbon tetrachloride. By cannulating the common duct it was possible to show that the fall in the prothrombin concentration which followed chloroform anesthesia started while bile salts were still present in the hepatic bile in good concentration, but was influenced in degree by sidetracking the bile to the exterior.⁶ It was also noted that animals which had had choledochostomy performed previously showed a greater fall in prothrombin concentration following chloroform anesthesia of given duration than did unoperated animals, and that a second anesthetization with chloroform, even after the prothrombin level had returned to normal, was followed by a much greater drop in the prothrombin concentration than was the first.

Liver damage due to chemical agents was associated with such prompt disappearance of prothrombin from the circulation that it seemed likely that certain agents actually exerted a deleterious action on prothrombin itself. In order to evaluate more accurately the rôle of the liver, total hepatectomy was carried out by Warren and Rhoads⁷ on eight dogs. In some animals this was performed by the three-stage method of Mann and in others it was accomplished by one-stage methods. The animals prepared by the three-stage method survived longest. Prior to the final stage the prothrombin had already been depleted to a considerable extent, probably as the result of the previous changes in the circulation of the liver. The subsequent fall, however, was quite rapid. Neither hemorrhage, celiotomy for other purposes, nor three-hour periods of ether anesthesia were effective in producing this marked drop. As the prothrombin level fell following the one-stage operation as well as the multi-stage procedure, it seemed justifiable to conclude that the fall was due to a cessation in the formation of prothrombin and not to the accompanying cessation of the bile salt supply to the intestine. Andrus, Lord and Moore,⁸ independently, arrived at similar conclusions.

In view of the relatively gradual decline in the prothrombin level observed in bank blood, the rapid disappearance of prothrombin from the hepatectomized animal obviously requires some explanation. This is partly to be found in the observation that blood specimens stored at room temperature show more rapid declines in prothrombin concentration than they do in the refrigerator at 4° C, and similar specimens stored in an incubator at 37° C show a profound drop in 24 hours.

Andrus, Lord and Kauer⁹ have called attention to an additional factor in this decline. They demonstrated that blood coming from the lungs regularly contains prothrombin in lower concentration than does blood in the pulmonary artery, indicating that some destruction of prothrombin regularly occurs in the pulmonary circulation.

The available evidence, therefore, points to a continuous and relatively rapid disappearance of prothrombin from the circulation and a concurrent

formation of prothrombin which occurs mainly if not exclusively in the liver. Acute liver injury is, therefore, we believe, sufficient to produce a sudden and serious drop in the prothrombin level in contrast to the gradual declines characteristic of vitamin K deficiency.

The question of whether an excess of vitamin K can, at least in part, compensate for faulty liver function is an important one. In favorable cases a single milligram of 2-methyl-1, 4-naphthoquinone may suffice to restore a moderately reduced prothrombin concentration to normal. In other cases in our experience as much as 42 mg in 24 hours has failed. It has been the impression of several workers that increased doses of the vitamin have overcome prothrombin deficiencies that were resistant to the usual doses. If a mass action effect takes place one would expect that it would affect the normal liver as well as the damaged liver and that the administration of 2-methyl-1, 4-naphthoquinone to normal individuals would lead to an increase in prothrombin concentration above the average normal. With the aid of Dr. Robert Norris, an attempt was made to ascertain whether this could be accomplished in a group of miscellaneous surgical patients at the Pennsylvania Hospital. The dose was 6 mg per day. The results were essentially negative, though a slight shortening in the prothrombin time was observed. This does not, of course, prove that at subnormal levels an excess of vitamin K may not be advantageous, but the mass action hypothesis does lack this bit of supporting evidence. Much larger doses might, of course, have a different effect.

In three cases of hypoprothrombinemia, in which an increased dosage of vitamin K seemed particularly useful, blood transfusions were also given. The effect was too great to be accounted for by the prothrombin in the transfused blood and was accordingly credited, in part, to the added vitamin K. Tocantins¹⁰ has reported a similar experience from the Jefferson Hospital and postulated that 2-methyl-1, 4-naphthoquinone and blood transfusion might have a synergistic action. One can speculate that the added protein in the blood aids in improving hepatic function, or that it provides needed building material for prothrombin formation, or that prothrombin is composed of two or more substances, only one of which may require vitamin K for its formation. This fraction might ordinarily be the critical factor in governing prothrombin activity but in the vitamin K-fast patient another fraction contained in normal blood might become the critical factor.

The observations of a synergistic effect of transfusion and vitamin K, or its substitutes, on the prothrombin level of the blood have not been sufficiently numerous to exclude coincidence as the explanation, but they do point to one approach to the problem of the patient with hypoprothrombinemia who is resistant to vitamin K therapy.

A more fundamental approach to this problem, however, appears to lie along the lines of improving the condition of the liver prior to operation. On the basis of animal experiments, which have been reported by Doctor Ravdin¹¹ a diet has been made up for the preparation of patients with

suspected moderate or severe liver damage on his service at the Hospital of the University of Pennsylvania. The diet consists of 75 per cent carbohydrate, 20 to 25 per cent of protein and not more than 5 per cent of fat. The total caloric intake is of great importance and should exceed 2,500 calories per day. The diet is continued for seven to 14 days before operation whenever possible. Strenuous efforts must often be made to induce the patients to eat adequately, but with added vitamins and added bile which is lyophilized and given in capsules as suggested by Dr. Charles Johnston, it has usually been possible to succeed and to have the patient gain weight preoperatively. Sufficient time has not elapsed since this regimen was started to evaluate adequately its effect on the response of hypoprothrombinemic individuals to vitamin K. During the six months' experience we have had, however, it has been possible to raise the prothrombin concentration to an adequate level for operation in every case.

Figures 1, 2 and 3 illustrate how badly some of these vitamin K-fast patients need a regimen which will improve the condition of their livers. These are photomicrographs of livers obtained at autopsy from patients who had a fall in prothrombin in spite of active vitamin K therapy. None of these patients was operated upon. Whether diet could have helped them may be doubtful, but it seems almost certain that the occasional patient whose prothrombin level will remain at dangerously low levels after adequate dietary preparation and adequate vitamin K therapy will have a hopeless prognosis for other reasons also.

The experimental data, so far available, indicate that hypoprothrombinemia as it occurs in most patients, can be accounted for by an interference with the formation of prothrombin without postulating an accelerated destruction of prothrombin. Interference with prothrombin formation may be due to absence of vitamin K from the alimentary tract, faulty absorption of the vitamin from the intestine, which is most commonly due to an inadequate supply of bile salts, or impaired production of prothrombin due to hepatic damage.

From the clinical standpoint, a large majority of surgical patients with prothrombin deficiencies will respond satisfactorily to the administration of vitamin K and bile salts. Some of those with impaired liver function will respond poorly or not at all. There are three methods of treating this group of patients. The first is to increase the dose of vitamin K. This has not produced a satisfactory response in many of those patients who were not responsive to moderate doses. The second is to give transfusions of blood which should preferably be freshly drawn. Whether or not this has a synergistic action with vitamin K, it is a valuable method for obtaining a temporary rise in prothrombin concentration. The third method, which may be tried if time permits, is to endeavor to improve hepatic functional activity by dietary means in addition to the continued administration of vitamin K, for with improvement in the cellular activity the likelihood of a more favorable response to vitamin K therapy can hardly be doubted.

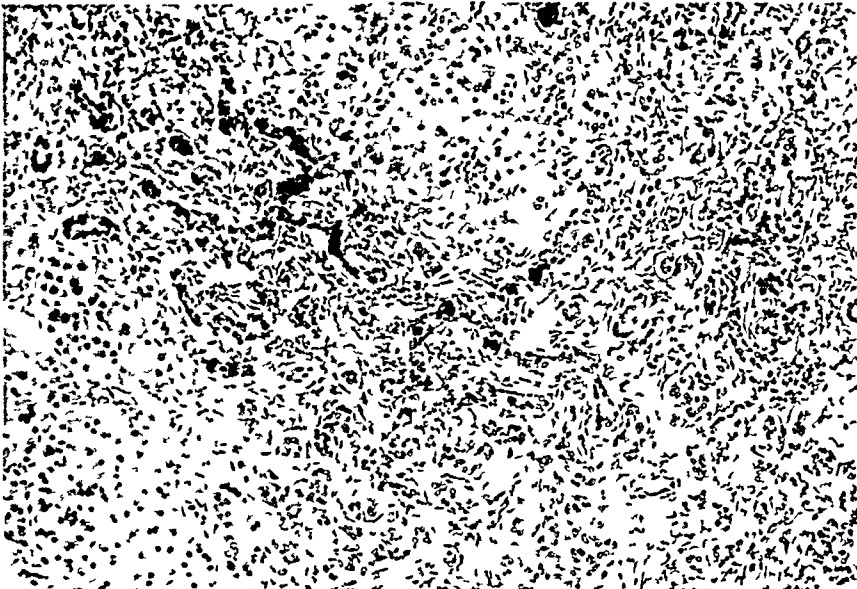


Fig. 1—Photomicrograph of section of liver of 4 months old child with atresia of the common bile duct who died 36 hours after a fall in plasma prothrombin concentration occurred in spite of the administration of 2 methyl 1, 4 naphthoquinone and bile salts. The hepatic parenchyma is largely replaced by fibrous tissue.

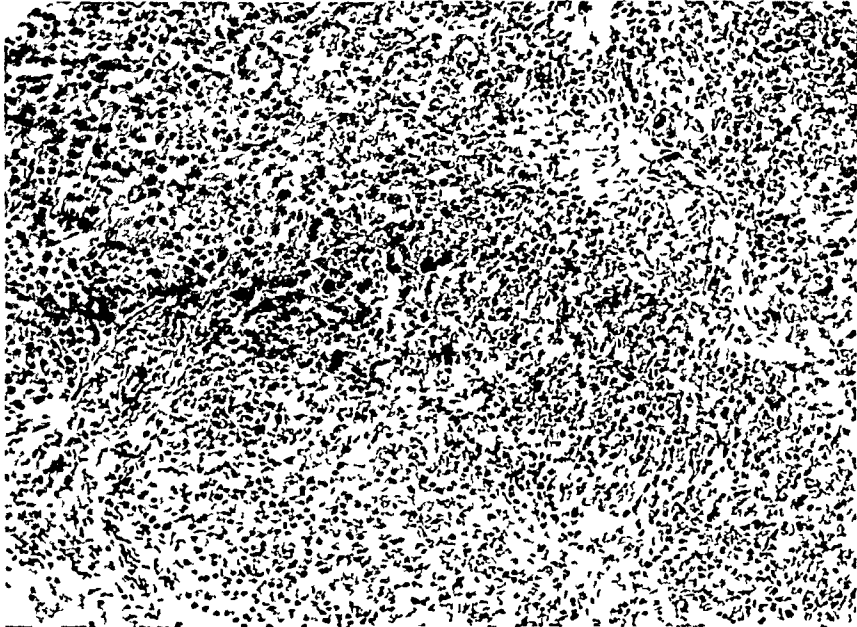


Fig. 2—Photomicrograph of section of liver of patient who died of carcinoma of the head of the pancreas. This patient's plasma prothrombin level was well controlled for several weeks but in spite of continued vitamin K therapy the level fell during the two weeks before death.

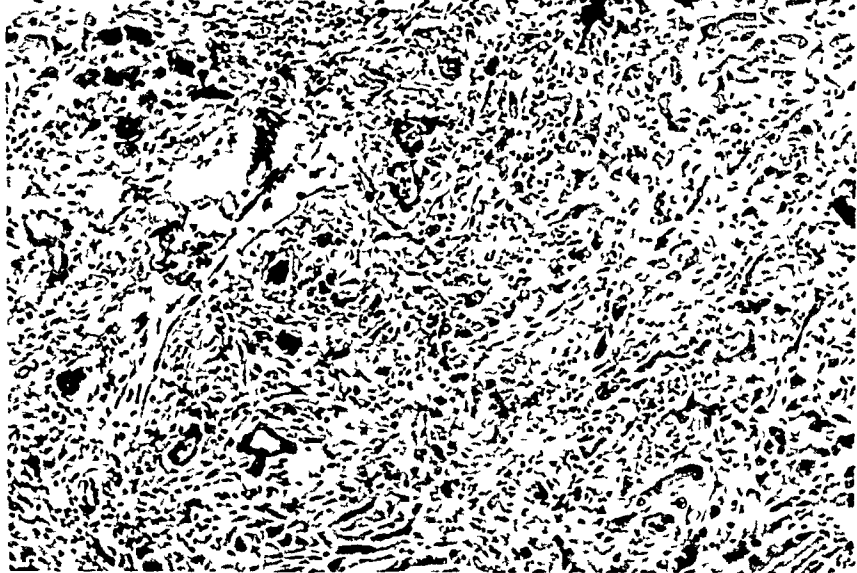


Fig. 3—Photomicrograph of section of liver of patient who died of carcinoma of the head of the pancreas. The prothrombin level fell shortly before death in spite of the oral and intravenous administration of 2 methyl 1, 4 naphthoquinone.

REFERENCES

- ¹ Quick, A J, Stanley-Brown, M, and Bancroft, F W Am Jour Med Sci, 190, 501, 1935
- Warner, E D, Brinkhous, K M, and Smith, H P Proc Soc Exper Biol and Med, 37, 628, 1938
- ² Quick, A J J A M A, 109, 66, 1937
- ³ Quick, A J J A M A, 110, 1658, 1938
- ⁴ McKee, R W, Binkley, S B, MacCorquodale, D W, Thayer, S A, and Doisy, E A Jour Am Chem Soc, 61, 1295, 1939
- ⁵ Rhoads, J E, and Warren, Richard To be published
- ⁶ Warren, Richard, and Rhoads, J E Am Jour Med Sci, 198, 193, 1939
- ⁷ Andrus, W deW, Lord, J W, Jr, and Moore, R A Surgery, 6, 899, 1939
- ⁸ Andrus, W deW, Lord, J W, Jr, and Kauer, J T Science, 91, 48, 1940
- ⁹ Tocantins, L M Personal communication
- ¹⁰ Ravdin, I S ANNALS OF SURGERY, 112, 576, 1940

DISCUSSION—DR WILLIAM DEW ANDRUS (New York City) It is a particular pleasure to hear Doctor Rhoads' paper and to follow the lines of thought in his presentation, as our own experience and line of thought have been similar. As he stated, we independently confirmed his finding that hepatectomy is followed by a very rapid fall in the plasma prothrombin, and we also showed that the administration of 10,000 units of vitamin K in the form of Klotogen and bile salts injected into the intestine at the time of operation failed to alter this fall in any way.

It is also extremely interesting that in the 49 cases which we have followed in our own series, in which we have used 2-methyl-1, 4-naphthoquinone, the percentage which failed to respond is exactly the same as in his.

Doctor Rhoads has brought up several very interesting points with regard to the physiology of the formation of prothrombin and the effect of liver damage upon it. The fact that the prothrombin cannot be elevated above 100 per cent of normal even by massive doses of the vitamin or of 2-methyl-1, 4-naphthoquinone is extremely interesting and can be very amply confirmed. We have given as much as 100 times—well, more than that—we have given to both normal and prothrombin deficient dogs of 10 Kg weight, doses of 50 mg of 2-methyl-1, 4-naphthoquinone, 1 mg being sufficient to produce adequate response in an adult, without in any instance being able to produce a rise of the prothrombin above the normal. What that is due to we do not know. A possible theoretic explanation is that if the naphthoquinone be the fundamental building stone of prothrombin, the liver has an upper limit above which it cannot manufacture prothrombin no matter how much of the raw material is available.

We had one very striking instance—a clinical case which Doctor Rhoads may have remembered I presented in discussing his paper last June—of a 50-year-old woman who had common duct obstruction and a very severe jaundice and inflammatory reaction about the base of the gallbladder. She responded strikingly to the administration of bile salts and vitamin K, her prothrombin returning to 100 per cent. Then, despite the continued administration of the same regimen, it suddenly fell down to 30 per cent and remained there until she died a few days later. At postmortem, she was found to have a thrombosis of the hepatic artery and portal vein with massive necrosis of the liver—if you will, a functional hepatectomy.

We have used intramuscular injections of 2-methyl-1, 4-naphthoquinone in 49 cases with diminished prothrombin level, with satisfactory response in 41. In three of these 49 patients, there was clinical evidence of liver dam-

age as indicated by liver function tests, but its exact nature is not yet known. In the five others, who failed to respond to 2-methyl-1, 4-naphthoquinone, and in two additional cases not included in the above series who were treated with Cerophil or Klotogen but whose prothrombin did not rise despite continued administration of the vitamin, the presence of marked liver damage was definitely proved—at operation in two cases and at postmortem examination in five cases.

These seven patients presented a wide variety of pathologic pictures, including Laennec's cirrhosis, cholangitis, periportal hepatitis, multiple liver abscess complicating pylephlebitis, gas bacillus infection, cirrhosis with central necrosis, and massive infarction of the liver secondary to the thrombosis of the hepatic artery and portal vein. The lesions were so diverse in nature and so widespread in extent as to yield little information regarding any specific type of liver injury responsible for the decreased prothrombin production.

In conclusion I should like to emphasize another point that Doctor Rhoads has made. We have here in its reaction in formation of prothrombin, which is interfered with in the presence of liver damage, a further reason for fortifying the liver by means of a high carbohydrate and high protein diet, if time permits before operation. In any event, doses of glucose should be given before operation, in order to stave off, liver injury which may play a very vital rôle in the prothrombin metabolism as it does in other respects.

HYPOPROTEINEMIA AND ITS RELATION TO SURGICAL PROBLEMS [†]

I S RAVDIN, M D

PHILADELPHIA, PA

FROM THE HARRISON DEPARTMENT OF SURGICAL RESEARCH, SCHOOLS OF MEDICINE, UNIVERSITY OF PENNSYLVANIA
PHILADELPHIA, PA

DURING the past two decades innumerable papers have been written on the fluid and electrolyte loss in persistent vomiting, in diarrhea, following extensive superficial burns, and in many other conditions, but until very recently, with the exception of the papers dealing with shock following trauma, very little has appeared in clinical literature on the important part that an adequate concentration of the plasma protein plays in keeping fluid in blood vessels. No consideration of fluid and electrolyte loss and their restitution is sufficient unless the plasma protein is simultaneously considered. The present symposium on a surgical program is evidence of the recognition by surgeons of the importance of plasma volume in a wide variety of conditions. The clinical and experimental conditions to be briefly considered in this paper may seem to be unrelated. Indeed, in some cases the studies were initiated independently. Nevertheless, a common factor would seem to appear as an important casual agent in each. This factor is the protein of the body available to meet the body's demands under the prevailing conditions.

General Considerations—Many of the patients coming to the surgeon for operation have, as a result of restriction of diet resulting from a variety of causes, from visceral injury, or from excessive plasma loss, a reduction not only in the concentration of plasma protein but also in the total available plasma protein. In fact, a reduction in the total plasma protein usually occurs before a reduction in the concentration takes place. Even though the concentration of the plasma protein is normal when the patient is first seen, it frequently falls sharply when fluids are administered in attempting to overcome an existing dehydration. Observations we have made strongly support the concept that there is no such thing as a critical level of the plasma protein at which edema becomes manifest. As soon as the plasma protein falls below the normal concentration, fluid begins to leave the vessels resulting first in a latent, and, finally, when the accumulation of fluid in the tissues is great enough, in an evident edema.

Weech and Ling¹ have shown that the administration of large amounts of neutral sodium salts, such as sodium chloride, will intensify the edema normally occurring at the same level as the plasma protein. Thus, frank edema may be present in patients receiving excessive amounts of salt solution, whose plasma protein concentration is well above the so-called critical level of edema of 5.2 Gm per cent. In the presence of hypoproteinemia, attempts to restore a normal fluid and electrolyte balance, without at the same time

[†] Read before the American Surgical Association, St. Louis, Mo., May 1, 2, 3, 1940

increasing the colloid osmotic pressure by adding to the plasma protein, too frequently result only in adding to the extravascular fluid reservoirs

Although the final pictures may be similar, the primary factors involved in hypoproteinemia in many conditions are, of course, quite dissimilar. In extensive superficial burns the hypoproteinemia is the result of the excessive loss of plasma protein into the tissues. The hypoproteinemia associated with hepatic disease is no doubt due to a defect in protein synthesis, while the hypoproteinemia encountered in gastric and duodenal ulcer and cancer results frequently from protein restriction in the diet. Thus, while a "loss or lack"² of protein accounts for many instances of hypoproteinemia, alterations from the normal of protein synthesis are also a factor in some conditions.

The evidence now available shows that in starvation or on diets low in protein the protein content of certain viscera, especially the liver,³ is markedly reduced. Whatever the cause of the reduction in total plasma protein, it is unlikely that this reduction is not also associated with at least a partial depletion of the important stores of rapidly mobilizable protein of the body. In protein undernutrition the tissue stores of protein may suffer before hypoproteinemia is excessive. The stores of protein mobilized under these conditions have been designated by Whipple⁴ as "labile protein."

When adequate protein feeding is begun the depleted stores of visceral protein must be at least partly replenished during the period of plasma protein regeneration. Tissue and plasma protein depletion and regeneration must, therefore, under many conditions go on simultaneously, the one complementing the other. In dogs which we had kept on an extremely low protein intake and further reduced their protein reserves by plasmaphereses, we obtained evidence which suggests that intravenously injected plasma protein was used for replenishment of protein stores depleted during the period of protein starvation.

During undernutrition, tissue protein is protected in part as long as carbohydrate and fat are available for energy requirements. The sparing action of carbohydrate on protein is too well known to require further discussion.

The many references in surgical literature to tissue regeneration upon a diet composed entirely of carbohydrate demonstrate a fundamental lack of knowledge of cell regeneration, for tissue growth requires protein components, the amino-acids, or larger aggregates, for building material.

Hypoproteinemia and Its Effect on Gastro-intestinal Motility—As Starling⁵ pointed out many years ago, the osmotic pressure of the plasma crystalloids, although large when compared with that of the plasma protein, is of minor importance in keeping fluids in blood vessels, for the crystalloids pass freely in either direction through the walls of blood vessels. As the plasma protein concentration falls from the normal 7.0 to 7.5 Gm per cent the osmotic pressure exerted by the plasma is reduced and fluid begins to leave the vessels, causing at first a latent and finally, when the increase of extravascular fluid is great enough, an evident edema. Jones and Eaton⁶ and Jones,

Eaton and White⁷ first called attention to certain complications which may occur during hypoproteinemia and its accompanying edema

The papers of Jones, Eaton and White,^{6 7} and those which we have published,^{8, 9, 10} focused attention on the importance of nutritional edema in gastro-intestinal surgery. The increase in subcutaneous fluid in hypoproteinemia is but one manifestation of a widespread increase in tissue fluid and the gastro-intestinal tract is not exempted from this process. McCray, Baiden, Frazier and I^{8 9 10} have shown that even when the gastro-intestinal tract of the dog is intact, a reduction in the plasma protein concentration will result in a marked increase in the normal gastric emptying time and a further delay in cecum appearance time. We have in a number of instances after operation upon our own patients, and in patients operated upon by other surgeons, found that the retardation of gastric emptying time may be so prolonged as to simulate a technical defect in the anastomosis. We have in fact, come to the conclusion that so-called "vicious circle" more often results from a disturbance in the normal movement of fluids than from technical defects of the new anastomosis.

In dogs, which many months previously had had a pylorectomy with restoration of gastro-intestinal continuity by the Polya technic, a reduction in the plasma protein by diet and plasmaphereses results in a marked increase in gastric emptying time. The roentgenographic appearance in these dogs, following the barium meal, is similar to that observed in many of the patients who supposedly have retention from a defect in the anastomosis after a similar operation.

The prolonged interference with a normal diet which many of the patients coming to operation for gastric and duodenal ulcer and gastric cancer have had, results, frequently, in varying degrees of undernutrition. The total caloric intake and the composition of the diet have very often been inadequate. The protein starvation may be the result of a self-imposed diet, but we have been impressed with the frequency with which hypoproteinemia has been observed while patients were under supposedly competent medical care. In man, the problem has been further complicated by the fact that there are frequently associated deficiencies in certain of the important accessory food-stuffs which affect gastro-intestinal motility and pattern.

Hypoproteinemia intensifies the edema of trauma naturally occurring at the site of gastro-intestinal suture. Under normal conditions of fluid exchange the edema of trauma begins to disappear 48 to 72 hours after operation, but in the presence of hypoproteinemia it continues to increase during this period, resulting in a mechanical impediment to the forward progress of the gastric contents.

Furthermore, when gastric contents pass into the small bowel the progress is further restricted by a coincidental, though less marked, decrease in small intestinal motility.

Surely, the convalescence of these patients will be smoother and the incidence of untoward complications will be reduced if nutritional deficits

are, if possible, corrected prior to operation, or as soon as possible after operation

I shall not discuss the many methods which may be employed both before and after operation to correct protein deficiency. At present we have found that the most rapid means of correcting it is by repeated plasma transfusions. These are well tolerated and rarely associated with the postinjection reactions so frequently observed after employing serum. We believe that it is better to administer small amounts of plasma repeatedly, over a long period, than to inject large amounts during a very short period. When more time is available and after operation upon patients whose "labile stores" of protein are thought to be very low, the orojejunal method, which Stengel and I^{11, 12} have described, is useful and practical. Although we have used varying amounts and combinations of amino-acids, intravenously in these patients, we have as yet no significant data that their administration in this manner will lead to the rapid synthesis of plasma protein. Even though we have, in a few instances, in the dog and in man obtained a positive nitrogen balance for a brief period, we have never observed a significant rise in the plasma protein concentration or the total plasma protein unless these substances were placed directly into the gastro-intestinal tract. Is the older viewpoint, that the gastro-intestinal mucosa conditions the amino-acids for protein-building stores, perhaps the correct one?

Wound Healing—In a study of wound healing which Smelo¹³ made in my department, in 1935, he concluded that "factors other than the local dressing appear to play the dominant rôle in determining the rate of wound healing." Anderson,¹⁴ continuing these studies, stated that "the healing of granulating wounds under normal conditions, as determined by precise volume measurements, occurs according to a regular geometric curve which may be expressed as a function of area and time, by the mathematic equation presented by Carrel¹⁵ and DuNouy¹⁶ for the normal cicatrization of clean surface wounds."

That disruption is still encountered in wounds free from infection, in which hemostasis was excellent, in which trauma to tissues and tension was minimal, and unusual strain obviated, strongly supports the concept that other factors of a general character play an important part in the failure of certain wounds to heal. That purely local factors may intensify the factors of a biologic character will not be doubted by anyone who has carried on investigations in this field.

We have shown that dogs which have been made hypoproteinemic by prolonged feeding of a low protein diet and plasmapheresis have a marked delay in fibroblastic proliferation and thus wound healing is retarded. The hypoproteinemia in our animals was but one manifestation of the protein starvation of the dogs. Although at first we were inclined to attribute the delay in fibroblastic proliferation to the presence of edema, we are now convinced that the mechanism is associated with a profound disturbance in protein metabolism, the hypoproteinemia being only an easily measurable indi-

cator of the extent to which the so-called "labile stores" of protein have already suffered

It is well known that cellular repair and regeneration require protein, for in the absence of an adequate amount of certain essential amino-acids growth cannot take place. Admont Clark¹⁷ has shown that on a diet high in protein there was no quiescent period in the repair of wounds, and Harvey and Howes¹⁸ have shown that such a diet causes accelerated fibroblastic proliferation. Without adequate building stores repair cannot take place.

A protein deficiency is of course not the only mechanism resulting in wound disruption. Sokolov¹⁹ and Lanman and Ingalls²⁰ have shown that a vitamin C deficiency is also an important biologic factor in this complication. These two nutritional disturbances are frequently found in patients who come for operations for gastric ulcer and cancer, duodenal ulcer, and biliary tract disease. That plasma may be employed to restore depleted protein stores was indicated in the experiments in which we gave large amounts of plasma, as much as 2,400 cc during a two-week period, to hypoproteinemic dogs that had been on a low protein diet for some days. The amount of plasma which we administered intravenously was more than six times the calculated plasma volume of the animal, but the plasma protein concentration never exceeded the original normal level for the dog. With the restoration of a normal serum protein concentration and, very likely, a more nearly normal store of tissue protein, the wounds promptly healed. Addis,³ and Holman, Mahoney and Whipple²¹ have shown that plasma protein can be utilized to replenish the depleted stores of tissue protein, and it is this purpose we believe that the excess protein, we injected, fulfilled.

When all the local factors favoring wound disruption are controlled, there will remain wounds whose failure to heal must be due to more widely acting causes such as hypoproteinemia and a reduction in "labile protein" stores, and deficiencies in important accessory foodstuffs.

Protein and Its Influence in Preventing Visceral Injury—In a study of the protective action of oxygen against liver injury, when certain hepatotoxic anesthetics were employed, our attention was directed to the relation of the dietary regimen to the susceptibility of the liver to damage by these same agents. That a diet high in carbohydrate is protective and that a diet high in fat induces maximal susceptibility of the hepatic cells when the liver is exposed to chloroform, has been repeatedly confirmed since the original reports by Opie and Alford.²² Experiments which Goldschmidt, Vais and I²³ have reported strongly suggest that glycogen *per se* does not protect the liver from the injurious effects of chloroform. Chemical analyses of the livers of animals following various diets, which were considered adequate and where feeding was prolonged, together with histologic evidence of changes in the cytology of the liver cells, have provided data which must lead to a realignment of our concept of the mechanism by which diet protects the liver or increases its susceptibility. It furthermore may, by inference, lead to certain conclusions on the effect of diet on regeneration.

The data which Goldschmidt, Vars and I²³ obtained conclusively demonstrated that, regardless of the reasons for the toxic action of chloroform upon the cells of the liver, the incidence and degree of injury increases with increases in the concentration of lipid in the liver. The data reveal no evidence that the level of hepatic glycogen *per se*, at the time of anesthesia, influences the toxic action of chloroform.

The hypothesis which assumes that glycogen *per se* is effective in protecting the liver against the action of chloroform received no support from our experiments. The data on the incidence and severity of damage to the liver with high and low contents of glycogen were essentially the same where the content of lipid was similar. There can be no doubt but that the susceptibility of the liver to injury by chloroform is markedly enhanced by the presence of small increments of fat.

On the other hand, when animals had been fed diets with a relatively high or low content of protein in the rations, and where the lipid concentration was similar, a striking protection was observed in the rats which had been provided 17 per cent or more of their total caloric value from protein. The significant difference is to be found in the severity of the cellular changes, for in the high protein group areas of necrosis in the liver were found in but 41 per cent of the rats, while in the low protein group extensive necrosis was present in 88 per cent of the rats. Although a high protein diet did not markedly influence the total incidence of hepatic injury, it decidedly reduced the degree of injury. The protective action of protein revealed itself even in animals with a high concentration of hepatic lipid and a low concentration of hepatic glycogen. The incidence of hepatic injury in starved rats was compared with that which was found in fed animals with the same initial hepatic fatty acid concentration. The extent and severity of the damage to the liver in the starved animals was almost maximal and nearly as great as that which we had observed in fed animals with approximately 50 per cent concentration of hepatic lipid.

That a high carbohydrate dietary regimen is efficacious in preventing liver injury is agreed to by every clinician who has administered such a diet in patients with hepatic disease. It would seem that the explanation of its action must lie in some concomitant effect produced by large deposits of hepatic glycogen. Rosenfeld²⁴ has found that under many conditions of the body, depletion of hepatic glycogen is followed by an increase in fat in that organ and vice versa. Opie and Alford²² suggested that the necrosis produced by chloroform, phosphorus and similar substances is perhaps the anatomic expression of advanced disintegration of body protein. Carbohydrate may, therefore, also be of value in limiting the necrosis due to these agents, by exerting its recognized function of sparing body protein.

The comparative protective value to the liver of foodstuffs against necrotizing anesthetics resolves itself, therefore, into the positive action of dietary protein versus the increased susceptibility to injury with increments in the hepatic lipid. In contrast to the indirect protection afforded by carbo-

hydrate the protection afforded by protein would seem to be a direct one, perhaps related to some intrinsic value of the protein itself

The data which we have collected have led us to postulate that a liver high in lipid content and low in protein is maximally susceptible to injury, a liver low in fat and high in protein is maximally protected from injury. Carbohydrate is advantageous only if, during its deposition in the liver, fat is displaced and if, as a result of an adequate store of hepatic glycogen, hepatic protein is spared.

Protein stored or elaborated into the body tissues may serve to protect the hepatic cells or to offer protein for regeneration should damage occur. The increased susceptibility of the starved animal is in our opinion chiefly a matter of depletion of its easily mobilizable protein stores.

Even so great an advocate of the carbohydrate protective concept as George Whipple²⁵ has recently confirmed our findings, and his associates²⁶ have extended them, for they have shown that a high protein dietary regimen protects the liver from the necrotizing effects of asphenamine. It is highly likely that a protein deficiency in the organism, frequent in surgical patients, either with or without hypoproteinemia, may lead to hepatic and other visceral injury following the use of a wide variety of hepatotoxic agents.

The evidence which we have brought forth, fortified by the recent investigations of Miller and Whipple,²⁵ and his associates, Messinger and Hawkins,²⁶ makes it highly probable that a carbohydrate-protein diet should be given in the future before operation whenever possible, and begun again after operation as soon as the gastro-intestinal tract will tolerate food.

Johnson, Vais, Zintel and I²⁷ have found that in the dog with a high lipid content in the liver, a diet consisting of approximately 72 per cent of the calories as carbohydrate, and 28 per cent as protein, was twice as efficient in reducing the concentration of hepatic lipid as carbohydrate alone given in the same number of calories per kilogram per day. If minimal visceral injury is to be conditioned and repair facilitated, an adequate amount of protein must be added to an otherwise satisfactory caloric intake.

CONCLUSIONS

An attempt has been made to demonstrate that a protein deficiency may be of serious significance in surgical patients. The reduction of the plasma protein, both in concentration and total amounts, frequently is associated with a reduction in the amount of protein stored in certain viscera. A reduction in the concentration and total amounts of the plasma protein as well as the so-called "labile stores" of body protein may result in the failure of a newly formed gastro-enteric or intestinal anastomosis to function normally, to impairment of normal fibroblastic proliferation and to increased susceptibility of certain viscera to damage by hepatotoxic agents.

BIBLIOGRAPHY

- ¹ Weech, A. A., and Ling, S. M. *Jour Clin Invest*, 10, 869, 1931
- ² Melnick, D., and Cowgill, G. R. *Yale Jour Biol and Med*, 10, 49, 1937

- ³ Addis, T, Poo, L J, and Lew, W Jour Biol Chem, 115, 111, 1936
- ⁴ Whipple, G H Amer Jour Med Sci, 196, 609, 1938
- ⁵ Starling, E H The Fluids of the Body The Herter Lectures New York, 1908
Chicago, W T Keener and Company, 1909
- ⁶ Jones, C M, and Eaton, F G Arch Surg, 27, 159, 1933
- ⁷ Jones, C M, Eaton, F G, and White, J C Arch Int Med, 53, 649, 1934
- ⁸ Mecray, P M, Jr, Barden, R P, and Ravdin, I S Surgery, 1, 53, 1937
- ⁹ Ravdin, I S Penn Med Jour, 41, 695, 1938
- ¹⁰ Barden, R P, Ravdin, I S, and Frazier, W D Amer Jour Roent and Rad Therapy,
38, 196, 1937
- ¹¹ Stengel, A, Jr, and Ravdin, I S Surgery, 6, 511, 1939
- ¹² Ravdin, I S, Stengel, A, Jr, and Prushankin, M J A M A, 114, 107, 1940
- ¹³ Smelo, L S Arch Surg, 33, 493, 1936
- ¹⁴ Anderson, D P ANNALS OF SURGERY, 108, 918, 1938
- ¹⁵ Carrel, A Proc Inst Med, Chicago, 8, 62, 1930, Jour Exper Med, 36, 385, 1923,
with Ebeling, A H Jour Exper Med, 34, 317, 1921
- ¹⁶ DuNouy, P L Jour Exper Med, 24, 451, 1916
- ¹⁷ Clark, A H Bull Johns Hopkins Hosp, 30, 117, 1919
- ¹⁸ Howes, E L, and Harvey, S C ANNALS OF SURGERY, 102, 941, 1935, Jour Exper
Med, 5, 577, 1932, ANNALS OF SURGERY, 91, 641, 1930
- ¹⁹ Sokolov, S Ergebn d Chir u Orthrop, 25, 306, 1932
- ²⁰ Lanman, T H, and Ingalls, T H ANNALS OF SURGERY, 35, 893, 1937
- ²¹ Holman, R L, Mahoney, E P, and Whipple, G H Jour Exper Med, 59, 269, 1934
- ²² Opie, E L, and Alford, L B J A M A, 62, 895, 1914, Jour Exper Med, 21, 1, 1915,
Jour Exper Med, 21, 21, 1915
- ²³ Goldschmidt, S, Vars, H M, and Ravdin, I S Jour Clin Invest, 18, 277, 1939
- ²⁴ Rosenfeld, G Alleg Med Zent Zeit, 89, 1051, 1900, Ergebn d Physiol, 2, 50, 1903,
Berl klin Wchnschr, 41, 587, 1904, Berl klin Wchnschr, 43, 978, 1906, Berl klin
Wchnschr, 47, 1268, 1910
- ²⁵ Miller, L L, and Whipple, G H Am Jour Med Sci, 199, 204, 1940
- ²⁶ Messinger, M D, and Hawkins, W B Am Jour Med Sci, 199, 216, 1940
- ²⁷ Johnson, J, Ravdin, I S, Vars, H M, and Zintel, H A The Effect of Diet upon
Liver Composition in the Presence of Common Duct Obstruction Arch Surg, 40,
1104, 1940

FLUID AND NUTRITIONAL MAINTENANCE BY THE USE OF AN INTESTINAL TUBE *

W OSLER ABBOTT, M D

PHILADELPHIA, PA

FROM THE CASTRO INTESTINAL SECTION (KINSEY THOMAS FOUNDATION) OF THE MEDICAL CLINIC, HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA, PA

THE MAINTENANCE of the fluid balance and nutritional state of a patient with an obstruction of the alimentary canal is made easier by the use of a rubber tube, but the manner of its use is diametrically opposite in the upper as compared to the lower end of the tract. When the esophagus or the pylorus is blocked, the tube may be surgically inserted below the lesion. Food is injected through it and the residue is passed by rectum. When the small intestine or colon is obstructed, the tube may be swallowed to the point of obstruction and through it may be withdrawn the residue of food which is eaten normally. Thus the nutritional problem in the high obstruction is to prepare a food that can be injected and will be tolerated by the digestive tract, in the low obstruction it is to find an adequate diet the residue of which can be withdrawn.

The problem is relatively simple in esophageal cases because the stomach tolerates a wide difference in the composition of its contents, and long experience with gastrostomies has shown that any feeding containing a reasonable balance of protein, fat, carbohydrate, vitamin, minerals and water will meet the requirement.

Jejunal feeding after the surgical relief of a pyloric obstruction is, however, a far more debatable subject. First, because it is not generally thought to be advisable, second, because the technique is less standardized, and, third, because the jejunum is a far more sensitive organ than the stomach and less tolerant of random feeding mixtures.

No one, to my knowledge, advocates jejunal feeding after every gastroenterostomy. On the other hand, patients with slowly stenosing pyloric lesions whose emaciation has become marked, before an episode of intractable vomiting brings them to the surgeon, present such a grave nutritional problem that one is impressed more by the fact that standard measures are so often successful than by the frequency with which failure results. The problem is intensified, moreover, by the common practice of keeping the stomach empty for another three or four days after operation. During this period, water, salt, and carbohydrates are given in abundance intravenously, but the protein intake is limited to that which can be administered by transfusion, and the total caloric intake rarely attains 800 per day. The work of Ravdin and his associates,¹ in particular, has, during the last few years, laid ample emphasis on the importance to the surgical patient of the protein intake. Not only does hypoproteinemia adversely affect wound healing, but

* Read before the American Surgical Association, St. Louis, Mo., May 1, 2, 3, 1940

many of the mechanical difficulties encountered at the gastro-enterostomy stoma, which were formerly thought to be due to errors in surgical technic, have been shown by them to be due to hypoproteimemic edema of the traumatized intestinal wall. The preceding speakers in this symposium have amply clarified the rôle which slight imbalance in the salt, fluid and protein intake can play in complicating the convalescence of these patients.

Noting the frequent use of intravenous infusion to sustain postoperative patients, and being impressed by the fact that the entire absorbing surface of the small intestine was available for tube feeding after a gastro-enterostomy, Andresen,² in 1918, began the practice of passing a Jutte tube into the jejunum at operation. The procedure, however, fell into disuse as appreciation of the im-

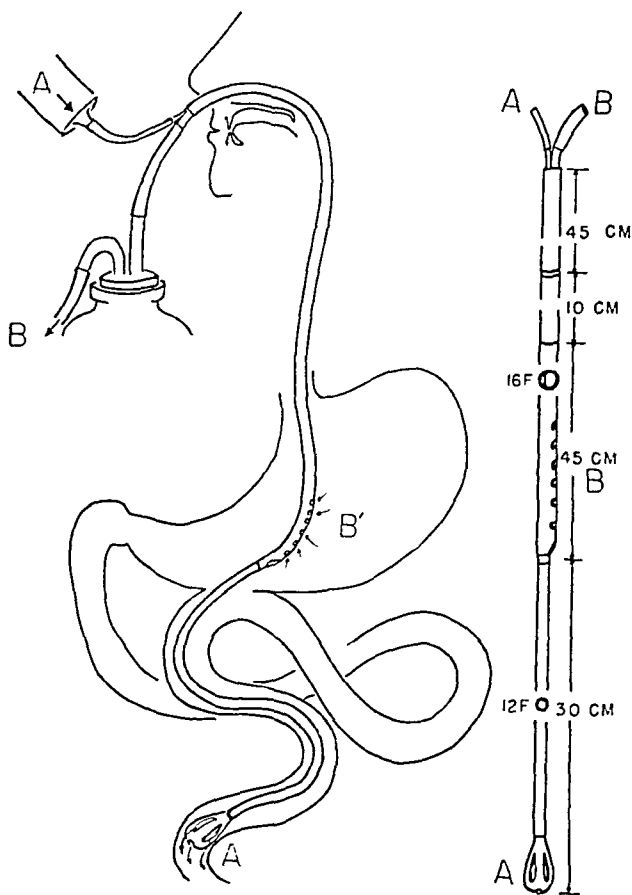


FIG 1—The gastro enterostomy tube in place (A) route of injection of nutrient solutions, (A') point of emergence of the solution, (B) attachment for the application of suction, (B') points from which contents are aspirated. (Reproduced from J A M A, 112, 2414, June 1939)

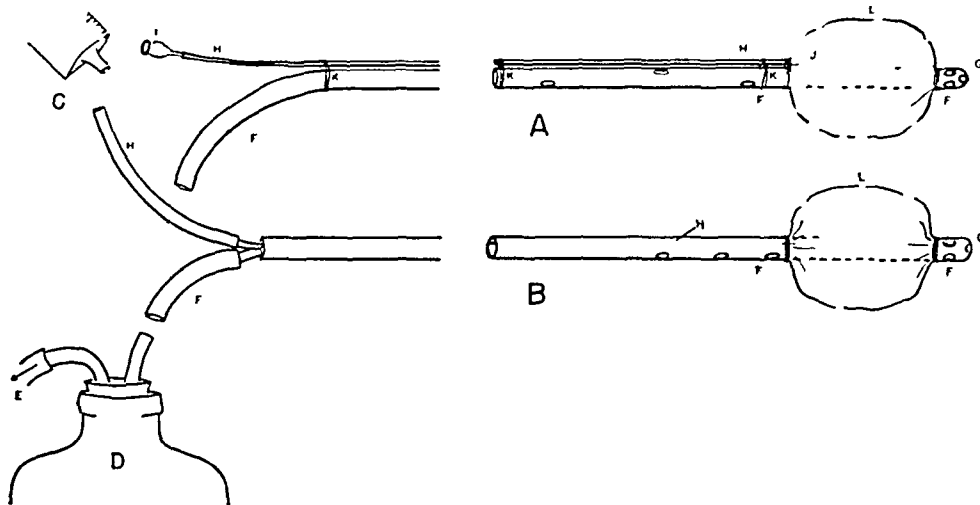


FIG 2—Small intestinal tubes arranged in a manner suitable for the treatment of acute intestinal obstruction (A) Constructed with two tubes fastened together, (B) constructed with one double lumen tube, (C) 50 cc glass syringe for filling the balloon (L), (D) bottle for collecting and measuring the aspirated intestinal contents, (E) tube leading to syphon bottles for maintaining suction, (F) passage through which intestinal contents flows, (G) any type of metal or rubber tip small enough to pass through the nose, (H) passage conducting air to the balloon, (I) hub of a No. 16 gauge needle to receive the syringe nipple, (J) a portion of the needle barrel inserted in the small tubing to facilitate tying on the balloon, (K) silk threads loosely tying the tubes together (L) about two and one half inches of rubber condom tied on with silk to form a balloon that can easily accommodate 30 cc of air. (Reproduced from Penn State Med Jour, 42, 890, May, 1939)

portance of an empty stomach after gastric surgery gained ground, and tubes, if passed at all, were used for aspiration purposes only. Rawson and I³ have met both requirements by using a double-lumened tube, one passage for gastric suction, one for jejunal feeding (Fig 1). The surgeon passes the tip through the stoma on completion of the anastomosis and 12 hours later jejunal feeding is begun. An extremely cachectic individual, dying after such a tube had traversed the suture line for 13 days, showed no gross or microscopic evidence of damage to the mucosa. The feeding can be given by drip, by the electrically controlled pump of Stengel and Vars,⁴ or by intermittent injection of 20 cc volumes with a syringe. The last method gives a slight stimulus to peristalsis which starts the distribution of the fluid down stream.

The feeding mixture must be prepared with the following points in mind, *viz* (a) The normal fasting jejunal contents are hypotonic,⁵ (b) the maximal glucose concentration that will normally enter the duodenum from the stomach is 15 per cent,⁶ (c) the maximal sugar concentration obtainable from the jejunum after glucose ingestion is 6 per cent,⁷ and, finally, (d) hyperperistalsis is produced by the introduction into the intestine of any glucose solution greatly in excess of these values.⁷ Glucose has been taken here as an example of the end-result of digestion. In general, the same is true of amino-acids and fatty acids. In a word, it seems desirable to predigest the food to avoid the risk of there being inadequate ferments for digestion in the sick patient, but the farther the process is carried the more irritant becomes the product, unless the concentration is correspondingly reduced. Thus, the more the predigestion the harder it becomes to increase the calories though it is possible that more of what is given is absorbed. That this is not an insurmountable problem is indicated by the very considerable success experienced by Stengel and Ravdin⁸ in elevating the serum protein level of these patients by the jejunal feeding of a casein hydrolysate. This is not yet on the market, however, and for the present acidified skim milk, incubated with commercial pepsin and fortified with 6 Gm of dextrose per 100 cc, and neutralized by the addition of sodium bicarbonate, gives a relatively high protein, high carbohydrate, and low fat feeding, that supplies about 1,500 calories in 2.5 liters. To this should be added, per day, 1 cc of viosterol in fish liver oil, 20 mg of thiamin chloride, 50 mg of nicotinic acid, and 100 mg of ascorbic acid. The food value of the mixture can be increased as the patient's tolerance permits.

This procedure, of postgastro-enterostomy jejunal feeding, has not yet been carried out in enough patients to allow the presentation of statistically valid evidence as to its worth in comparison with standard methods. Sufficient experience has been had with it, however, to warrant the statement that it is both practicable and practical.

A typical case is one from the series of Stengel and Ravdin.

Case Report—B. K., male, age 57, was admitted to the hospital, with a history of 15 years of "heartburn" and "bloating," especially after heavy meals. He habitually obtained relief by inducing vomiting or by taking sodium bicarbonate. Constipation was

persistently present Six months before admission he lost his appetite Though his weight loss was 20 pounds during the last four weeks before his admission, he stated that frank pain was of less than 24 hours' duration Vomiting had become spontaneous and frequent Examination revealed generalized upper abdominal tenderness without rigidity The initial impression of a duodenal ulcer was confirmed at operation but evidence of a previous small perforation was presented by the fibrinous exudate over the surface of the stomach and the firm adherence of small bowel to the anterior surface of the duodenum A posterior gastrojejunostomy was performed, and before closing the abdomen a double-lumened gastro-enterostomy tube was passed through the stomach into the jejunum

Before operation, he was dehydrated, and showed a plasma chloride level of 95.2 meq/L, and a plasma protein of 7.1 Gm per 100 cc Gastric suction was instituted at once, and jejunal feeding was started on the second postoperative day In spite of a transfusion both before and after operation, his plasma protein level had dropped to 5.3 Gm per 100 cc by that time During the next week he received no further transfusions, all his fluid being given by mouth or into the jejunum That which was taken by mouth was, in the main, drained out again promptly, serving chiefly to keep the mouth and throat clean and the stomach washed clear of mucus On the first day of jejunal feeding, the volume given was limited to 680 cc Thereafter, it varied from 1,794 to 2,274 cc per day At the end of this week the plasma protein was 6.7 Gm per 100 cc The feeding mixture used in this instance was an experimental casein hydrolysate being investigated by Doctors Ravdin and Stengel It contained 5 per cent of glucose as well as the split products of casein digestion From the standpoint of technic, however, it exemplifies the simplicity of a method that promptly makes available to the physician the normal route of absorption in a patient the nature of whose disease would otherwise force one to the use of more artificial procedures

Obstructions below the pylorus, involving the small intestine and colon, present a totally different problem from the nutritional standpoint, and here the use of the tube is reversed (Fig 2) Its primary purpose is to decompress the distended intestine and to tide the patient over an acute crisis If the obstruction is of such a nature that operation is necessary, the patient must be properly prepared for surgery from the fluid, electrolyte and serum protein standpoint, if the obstruction is of inflammatory origin, he must be kept in a good state of nutrition during the week or two which may pass before his bowels move⁹ There are two chief points of importance to be considered here First, to appreciate the extent to which his electrolyte reserves are being depleted by the constant drainage of his intestinal contents, second, to supply him with a diet that he can eat in spite of an inlying tube in his nose and throat, and that will yield a residue which can be drawn back through the tube

The most important element lost in the drainage from points below the duodenum and high jejunum is sodium chloride Too much has been said already about the causes and results of salt loss and the technic of its replacement to require amplification here Maddock¹⁰ has devised a formula for calculating the immediate salt replacement required when the patient is in a critical state It is a great help during the period of maintenance, however, to use the volume of drainage as the basis of calculation for salt replacement because it is so obviously quick and convenient Luckily, the concentration of salt loss is remarkably constant in the face of even widely varying amounts

of salt and fluid administered, without regard to the route of administration¹¹ Figure 3 shows that about 0.6 Gm per 100 cc not only represented the average of 67 determinations but it is apparent that little deviation from the average took place and that little variation occurred when collections were made from different levels in the bowel. Figure 4 shows the range of variation in an individual case. From this, the convenient conclusion may be drawn that sodium chloride, grains \times , given in capsules each time the patient drinks 100 cc of water will come very close to maintaining an intake of the same salt concentration as is present in the output by drainage.

SODIUM CHLORIDE LOSS IN DRAINAGE FROM OBSTRUCTED INTESTINE

5 PATIENTS

(Gm /100 cc)

	Analyses	Highest	Lowest	Average
Stomach, duodenum and jejunum	10	0.68	0.37	0.49
Ileum	49	0.81	0.38	0.61
Cecum	8	0.65	0.51	0.59
Total	67			0.58

10

Total
Distribution 5
Curve

0

39 44 49 54 59 64 69 74 79
Gm /100 cc

FIG 3 —Concentration of sodium chloride lost by intestinal drainage

Another bit of good fortune is apparent in considering the food requirement. The importance of a low residue has been stressed. Since the patient with intestinal obstruction may be in as great need of serum proteins as the patient with pyloric obstruction and for much the same reasons, it is fortunate that a high protein diet and a low residue diet are identical. The best study of dietary residue in this regard is still that of Hosoi, Alvarez and Mann.¹²

When a patient with a low obstruction is treated by the passage of a small intestinal tube, strained fluids should be started at once provided that salt is given as described. While the tube is in the stomach this constitutes gastric lavage. As soon as it traverses the duodenum the fluid begins to

THE USE OF AN INTESTINAL TUBE

contribute to his maintenance. When the tube is progressing down the jejunum strained soup, tea, coffee, melba toast, puffed rice and clear jellies are cautiously tried. To this may be added zwieback, Holland rusks, boiled rice, cream cheese, well cooked eggs and finally strained cereal, chicken and lean beef and lamb. Noer and Johnson¹³ have reported a very satisfactory dietary. On such a regimen the patient should be able to take 1,500 to 1,800 calories daily for two to three weeks in spite of complete obstruction if the nasal and throat irritation from the tube can be combated for that long a period.

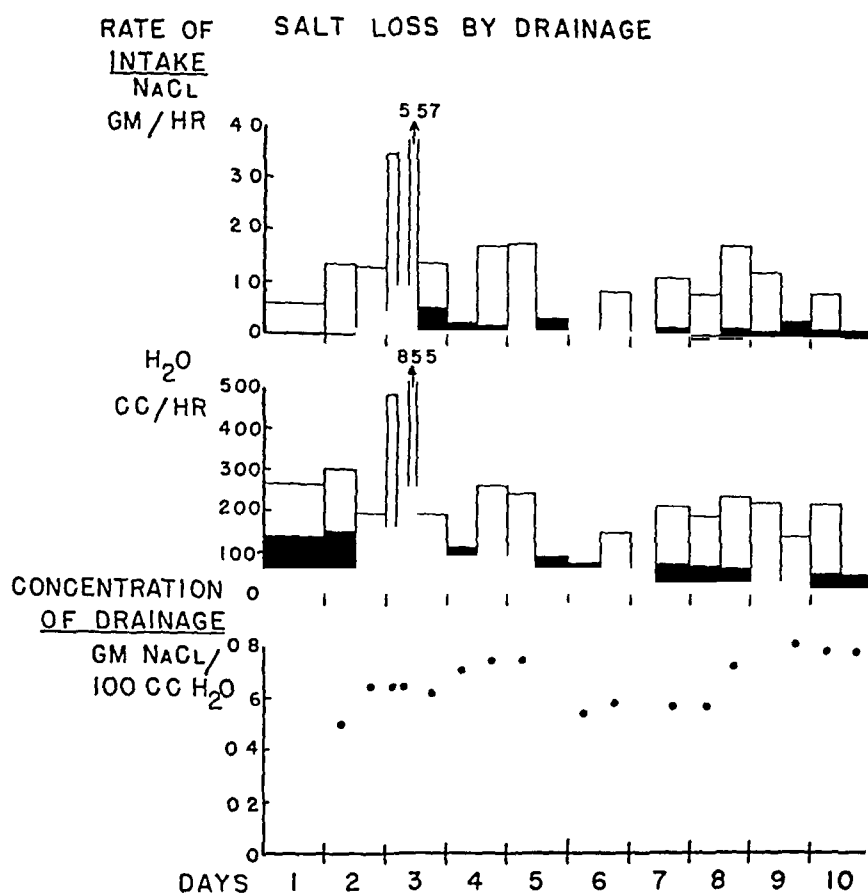


FIG 4.—Case E B. A postsplenectomy obstruction of the small intestine was constantly decompressed by aspiration of the small intestinal contents above the point of obstruction for ten days. Because of technical difficulties he could not be controlled satisfactorily and, therefore, required salt by mouth (black) and parenterally (clear) at totally irregular intervals. In spite of this, the salt concentration in the drainage did not vary more than 0.15 per cent from the usual average level of 0.6 Gm per 100 cc.

Under these circumstances his vitamin requirement may be met by the use of viosterol capsules, autolyzed brewer's yeast and orange juice in adequate amounts daily.

A typical case so treated is appended.

Case Report—J. R.,* white, male, age 58, steamfitter, was in good health till 2:45 P.M. when he was seized with a diffuse cramp-like pain in the abdomen while he was at work in the hospital. In retrospect, he afterwards recalled some vague abdominal distress

* Patient of Dr. E. L. Eliason.

during the preceding 48 hours but he had paid no attention to it. Within an hour, the pain had localized in his right lower quadrant, he began to vomit, and in less than two hours from the onset, operation had revealed a ruptured appendix with seropurulent fluid free in the peritoneal cavity. The wound was drained and he was given sulfanilamide. At the end of 24 hours, a Wangensteen tube was used because of distention. This was



FIG 5—Case J. R. Roentgenographic evidence of small intestinal obstruction

removed on the second day, and for the next six days the patient took liquids by mouth, but because of ill-defined distress on eating it was necessary to supplement this by intravenous infusions of glucose and salt solution. Peristalsis was present but was hypoactive till the sixth postoperative day when it became hyperactive and the patient vomited. This was repeated on the eighth day. The Wangensteen tube was reinstated but was again

THE USE OF AN INTESTINAL TUBE

removed on the ninth day because the patient was comfortable. On the eleventh day vomiting recurred, accompanied by distention. This rapidly increased and a gastrointestinal consultation was asked for on the thirteenth day. Although the patient passed one puff of flatus that day the clinical and roentgenologic evidence was of a mid small intestinal obstruction (Fig 5). A long intestinal tube was passed into the stomach by Dr Richard Warren, but for over two days neither he nor I could advance it into the small intestine. During that time it kept the stomach deflated and some decompression was accomplished by removing the reflux of small intestinal contents. The advisability

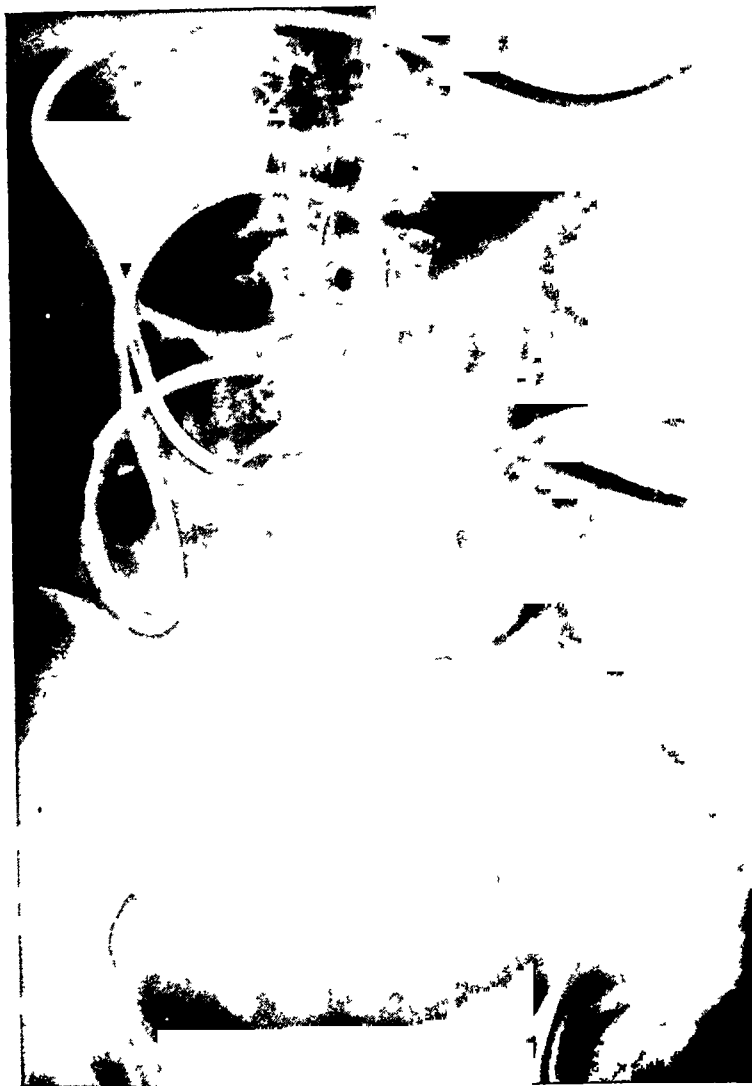


FIG 6—Case J R. Roentgenogram showing a tube descending the small intestine. The patient was taking fluid, salt and food by mouth. Decompression was not yet complete.

of performing an enterostomy was repeatedly discussed but on the third day Doctor Warren successfully introduced the tube into the jejunum and from then on decompression progressed rapidly. On the seventeenth day, the location of the obstruction was demonstrable by the injection of barium down the tube under the fluoroscopic guidance. One isolated segment of ileum remained out of reach of the tube for a time (Fig 6) but in the course of a few days the tip entered and emptied it also. On the twenty-first day a little feces was passed but it was not until the twenty-third day that the tube could be clamped off entirely. It was removed on the twenty-fifth day and convalescence continued normally with no subsequent evidence of obstructive phenomena in the year that has elapsed.

From the sixteenth to the twenty-fourth day the patient was, for all practical purposes, completely obstructed, though toward the last of this period he began to pass small quantities of feces per rectum. Intravenous infusions were administered occasionally but, from the nutritional standpoint, he derived most of his fluid, salt and calories from what he took by mouth. His nutrition was good when his appendix ruptured. During the first two weeks after operation he received far less than his basal caloric requirement. When intubated he was dehydrated, his serum chlorides were 89 m eq/L and his serum protein 6.8 Gm per 100 cc. Three days later he was hydrated, his serum chlorides were 96.6 m eq/L and his serum proteins 5.9 Gm per 100 cc. It is doubtful if the change in percentage concentration means anything more than increased blood volume. By mouth he received a diet of 1,200 calories in three meals to be chosen from the foods listed earlier. These foods were well salted and in addition he received salt in capsules as indicated. Two blood transfusions were given during his hospital stay. His vitamin requirement was adequate. He did not always eat the amount of food offered and on some occasions he vomited a portion of what he had eaten. Although this case could not be conducted as a balance experiment, it was the feeling of the staff that his state of nutrition was good when the obstruction disappeared. In support of this opinion was the fact that he was sitting up beside his Wangenstein bottles while still obstructed and was well enough to go home the day his tube was removed.

CONCLUSIONS

In the presence of high obstructions in the alimentary canal a tube may be placed by surgical means in such a position that food may be introduced into the tract below the obstructing lesion. When this food is placed in the stomach a wide leeway in its preparation is permissible. When the food is placed in the small intestine it must be very carefully prepared so that it will not be irritant from too little digestion on the one hand or from too much digestion on the other.

In the presence of low obstructions the tube is passed to the obstruction itself and is then used to recover the residue of food eaten normally. The point of importance under these circumstances is to supply those foods most needed by the patient and at the same time to avoid all foods the residue of which cannot be drawn back through ten feet of tubing.

BIBLIOGRAPHY

- ¹ Ravdin, I. S., Stengel, A., Jr., and Prushankin, M. The Control of Hypoproteinemia in Surgical Patients. *J A M A*, 114, 107-111, January, 1940.
- ² Andresen, A. F. R. Immediate Jejunal Feeding after Gastro-Enterostomy. *ANNALS OF SURGERY*, 67, 565, May, 1918.
- ³ Abbott, W. O., and Rawson, A. J. A Tube for Use in the Postoperative Care of Gastro-Enterostomy Cases. *J A M A*, 108, 1873, May, 1937.
Idem. A Tube for Use in the Postoperative Care of Gastro-Enterostomy Cases—A Correction. *J A M A*, 112, 2414, June, 1939.

- ⁴ Stengel, A, Jr, and Vars, H M An Apparatus for Continuous Intravenous Injections in Unanesthetized Animals Jour Lab and Clin Med, 24, 525, February, 1939
- ⁵ Karr, W G, and Abbott, W O Intubation Studies of the Human Small Intestine IV Chemical Characteristics of the Intestinal Contents in the Fasting State and as Influenced by the Administration of Acids, of Alkalies and of Water Jour Clin Invest, 14, 893, November, 1935
- ⁶ Karr, W G, Abbott, W O, Hoffman, O D, and Miller, T G Intubation Studies of the Human Small Intestine XIII The Concentration and Movement of Glucose Solutions in the Stomach and Duodenum Am J Med Sc, in press
- ⁷ Abbott, W O, Karr, W G, and Miller, T G Intubation Studies of the Human Small Intestine VII Factors Concerned in the Absorption of Glucose from the Jejunum and Ileum Am Jour Digest Dis and Nutrit, 4, 742, January, 1938
- ⁸ Stengel, A, and Ravdin, I S The Maintenance of Nutrition in Surgical Patients with a Description of the Orojejunal Method of Feeding Surgery, 6, 518, October, 1939
- ⁹ Miller, T G, and Abbott, W O Intestinal Intubation A Practical Technique Am Jour Med Sci, 187, 595, May 1934
- ^{9a} Abbott, W O, and Johnston, C G Intubation Studies of the Human Small Intestine X A Nonsurgical Method of Treating, Localizing and Diagnosing the Nature of Obstructive Lesions Surg, Gynec and Obstet, 66, 691, April, 1938
- ^{9b} Johnston, C G, Pemberthy, G C, Noer, R J, and Kenning, J C Decompression of the Small Intestine in the Treatment of Intestinal Obstruction J A M A, 111, 1365, October, 1938
- ^{9c} Leigh, P C, Nelson, J A, and Swenson, P C The Miller-Abbott Tube as an Adjunct to Surgery of Small Intestinal Obstructions ANNALS OF SURGERY, 111, 186, February, 1940
- ¹⁰ Maddock, W G Maintenance of Fluid Balance Am Jour Surg, 46, 426, December, 1939
- ¹¹ Abbott, W O Intubation Studies of the Human Small Intestine XII The Treatment of Intestinal Obstruction and a Procedure for Identifying the Lesion Arch Int Med, 63, 453, March, 1939
- ¹² Hosoi, K, Alvarez, W C, and Mann, F C Intestinal Absorption A Search for a Low Residue Diet Arch Int Med, 41, 112, January, 1928
- ¹³ Noer, R J, and Johnston, C G Decompression of the Small Bowel in Intestinal Obstruction Am Jour Digest Dis and Nutrit, 6, 46, March, 1939

PARENTERAL REPLACEMENT OF PROTEIN WITH THE AMINO-ACIDS OF HYDROLYZED CASEIN †

ROBERT ELMAN, M D

ST LOUIS, MO

FROM THE DEPARTMENT OF SURGERY, WASHINGTON UNIVERSITY AND THE BARNES AND HOMER PHILLIPS HOSPITALS
SAINT LOUIS MO

PARENTERAL REPLACEMENT of protein has become recognized as an important therapeutic need only during the past decade. This has been due largely to an increasing realization of the frequency and seriousness of hypoproteinemia in a variety of patients and in the apparent inability of the body to always correct this deficiency spontaneously. The problem is made more serious by the fact that transfusions frequently fail to correct the deficiency and for many other reasons, there is, in addition, a growing appreciation that protein needs other than those for the synthesis of serum protein may be important in many patients nutritionally depleted and unable to take and absorb nourishment adequately by mouth.

The possibility of supplying protein needs parenterally with amino-acids has been suggested from time to time, particularly by Rose,¹ in 1934, and was achieved experimentally as early as 1913 by Henricque and Andersen.² In the human, amino-acids were injected intravenously for purposes of protein alimentation for the first time in this clinic,³ the amino-acid preparation used at that time was a mixture obtained by acid hydrolysis of casein, fortified with tryptophane which is destroyed during digestion by acids. Evidence of utilization, experimentally and clinically, as well as therapeutic effects in patients, was observed.³ The necessity of adding tryptophane was, however, a disadvantage because of its cost.

The present observations are concerned with the injection of an enzymatic hydrolysate of casein,† containing *all* amino-acids present in casein, including tryptophane, and capable of maintaining nitrogen balance and promoting normal growth in rats.⁴ This preparation has the power of provoking serum albumin restoration in experimentally produced acute hypoproteinemia.⁵ Clinical observations in children have already been reported with this enzymatic product by Shohl, Butler, Blackfan and MacLachlan,⁶ and by Farr and MacFayden.⁷ Both of these groups of observers presented data indicating that the injected material was utilized. Although the former workers noted severe reactions (chills and fever) following the injection in several babies, the latter have injected large amounts without such reactions.⁸ Undoubtedly, this difference was due to differences in the manner of preparation of the solutions for intravenous use.

* Aided by grants from the Louis B. Beaumont Fund, and from Mead Johnson & Co. Read before the American Surgical Association, St. Louis, Mo., May 1, 2, 3, 1940.

† This material has been generously supplied by Mead Johnson and Company, Evansville, Indiana.

The enzymatic hydrolysate, though a complete mixture of amino-acids, is, I am told, not as easy to prepare as the acid hydrolysate because of numerous technical difficulties. Unlike the latter, the former product is not completely hydrolyzed, only two-thirds being in the form of amino-acids, the remaining third being in a more complex form, presumably dipeptides. It is, however, not anaphylactogenic for guinea-pigs, moreover, the incompleteness of the hydrolysis is apparently of no biologic significance. This enzymatic preparation of casein (called 92-Z) was used in all of the observations reported herein. It should be mentioned, however, that successive batches of this product have been used, each of which has represented improvements in the method of manufacture as shown by easier solubility and less tendency toward reaction when injected intravenously, even when given at a faster rate than earlier products.

Method of Administration—As received, the product is a dry, impalpable powder which is made up as a 10 per cent solution and heated to 90° C. For complete sterilization the solution is passed through a Seitz (EK) filter and 100 cc amounts poured into flasks containing 400 cc of sterile 10 per cent glucose, the mixture is then injected intravenously during one hour. Thus, in eight hours of continuous venoclysis (or two four-hour periods) 4,000 cc can be injected—containing 1,600 calories and 80 Gm of protein as amino-acids. Adequate electrolyte is also added, ordinarily as concentrated Ringer's solution—equivalent to 10 Gm of salt per day. The nitrogen concentration of the 10 per cent solution is 1.2 Gm per cent—so that when 4,000 cc are administered the patient receives 9.6 Gm of nitrogen. This is equivalent to the nitrogen in 3,000 Gm (nearly $\frac{3}{4}$ lb) of lean beef.

For injection the ordinary infusion flask has been used, the rate of flow being measured by the drops falling through an interpolated sealed glass trap. All connections were of glass and only stainless steel needles were used.

Difficulties Encountered—Most of the earlier difficulties have disappeared with successive improvements in the manufacture of the hydrolyzed casein. The solubility has increased, so that precipitation of the solutions is no longer encountered. Obviously, a perfectly clear solution must be maintained before the material can be administered intravenously. Another difficulty has been the phlebitis induced when long periods of venoclysis were required. It has been my impression that the more recent preparations of hydrolyzed casein have shown less tendency toward thrombosis. This tendency, however, is not very great with the dilute (2 per cent) solutions.

The most serious difficulty has proved to be the occurrence of occasional reactions, similar to those reported by Shohl, *et al*.⁶ Many patients had none even after two weeks of daily injections. In a few cases the reactions were undoubtedly due to the rapidity of injection. Thus, in Case 4, on March 24, 1939, 2,250 cc of a 10 per cent glucose solution, containing 2 per cent of product 92-Z, was administered in five hours without reaction, later in the day, 1,500 cc of the same solution was administered in two hours, and was followed by a chill and a temperature rise of 3° C. Whatever the cause of

reactions, there has been a complete absence, thus far, with the more recently received material. Indeed, the latest product (No 143, which has already been brought into solution by the manufacturer) has been injected into three patients at a speed twice as fast as that already mentioned. Thus, 1,000 cc, containing 10 per cent glucose, $2\frac{1}{2}$ per cent hydrolyzed casein, and 0.45 per cent NaCl, was given in one hour without reaction. In spite of the rapidity of the injection less than 0.1 Gm of amino-acids of the 25 Gm given appeared in the urine during the ensuing three hours. I believe that untoward reactions are due to one or more factors connected either with the manufacture of the hydrolyzed casein, with its method of solution and preparation for intravenous use, or with the technic of administration itself. These factors appear to be almost if not completely solved with the most recent product, only further experience will tell.

It must, of course, be admitted that uniformity in the composition of the amino-acid mixture is highly desirable if not essential. Whether such a uniformity can be or actually has been achieved is still incompletely answered and awaits further experience. Nevertheless, the preparation now available for experimental use has been administered to 35 patients, and data of much interest and great promise have been accumulated.

Clinical and Metabolic Observations—The mixture of glucose, amino-acids and electrolyte described above was administered to 35 adults as their sole source of fluid and food, the period of treatment varied from one to 23 days and averaged over ten days. The total daily dose varied somewhat, but in most cases a maximum amount of 80 Gm of 92-Z was given, this averaged between 1 and 2 Gm per Kg per day, dependent upon the body weight of the patient. As already mentioned, 80 Gm of the hydrolyzed casein contains 9.6 Gm of nitrogen. In 20 patients, nitrogen balance studies were carried out, complete collections of urine, feces and vomitus were analyzed for total nitrogen by the Kjeldahl method. Serum proteins were also determined in this way. The serum was fractionated by Howe's method. Of the following eight representative cases, the first two are normal controls, the next two preoperative and the last four postoperative patients.

REPORTS OF EIGHT REPRESENTATIVE CASES

Case 1—Hosp No D-7721. P. W., Negro, male, age 55, was admitted, November 1 1939 to the Homer Phillips Hospital. He was an asthmatic, and had been a patient many times previously with the complaint of respiratory distress. This time he complained more especially of epigastric pain and vomiting and had lost 20 pounds in weight. Examinations including cholecystogram and gastro-intestinal roentgenologic series were negative. All laboratory tests were negative, the serum protein was 7.01 Gm per cent, albumin 4.2 Gm per cent. Intravenous alimentation, with complete gastro-intestinal rest, was suggested and he accepted this regimen. During 15 days he took nothing but a little cracked ice by mouth, and was given each day 3,000 cc of 10 per cent glucose containing the equivalent of 1,000 cc of Ringer's solution, i.e. two ampules of concentrated Ringer's (each sufficient for 500 cc). After three days, a solution containing 60 Gm of amino-acids (92-Z) was added to the glucose (Fig 1). Only one reaction occurred during the intravenous therapy on the fifteenth day, when the patient had a slight chill but exhibited

PARENTERAL REPLACEMENT OF PROTEIN

no elevation of temperature Subjectively the procedure was well tolerated, the patient's epigastric pain disappeared completely and when he was put on a regular diet it did not recur He left the hospital asymptomatic and returned three months later with a request for a repetition of the experience

Case 2—Hosp No D-5541 Z C, Negro, male, age 65, was admitted, November 5 1939, to Homer Phillips Hospital He was a frequent patient in the hospital, the diagnosis each time being bronchial asthma and hypertension, the electrocardiogram showed advanced myocardial damage He had lost some weight and complained of difficulty in swallowing although all examinations including a cholecystogram and gastro-intestinal roentgenologic series were normal Laboratory tests were all normal, the serum protein was 7.2 Gm per cent, albumin 3.3 Gm per cent A period of complete gastro-intestinal

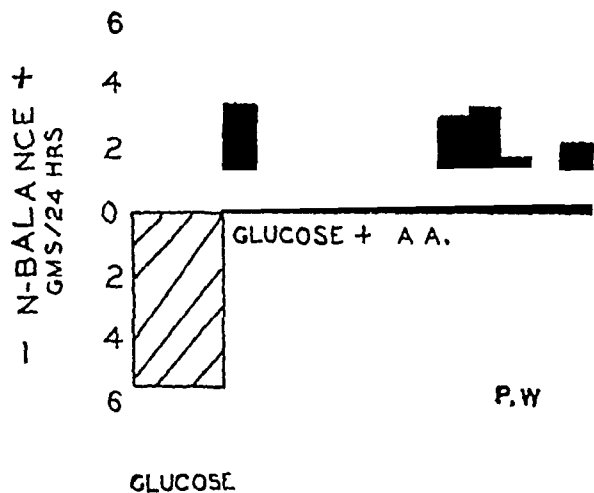


FIG 1

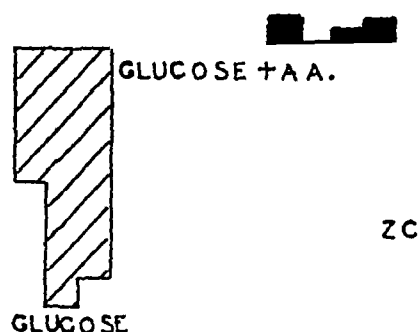


FIG 2

FIG 1—Case 1 and FIG 2—Case 2. In both cases represented above the gastro-intestinal tract was normal (see Case Reports). Note, in both, the immediate achievement of positive nitrogen balance when amino acids were added to the intravenous glucose. The cross hatched columns represent the nitrogen output during three days during which 3,000 cc of 10 per cent glucose was injected daily. The solid black represents the period during which 60 Gm of hydrolyzed casein (7.2 Gm N) was added daily. The metabolic study in Case 1 lasted 15 days, in Case 2, 12 days.

rest was suggested to him, which he accepted. For 12 days he was given only cracked ice by mouth and 3,000 cc of 10 per cent glucose plus Ringer's solution for three days, and then amino-acids were added (Fig 2) as described in Case 1. He had no reactions whatever during the experiment and complained of no hunger. When he was returned to a regular diet he was able to eat better and left the hospital much improved.

Case 3—Hosp No 73309 G A H, white, male, age 48, was admitted, March 10, 1939, to Barnes Hospital. He had had several abdominal operations elsewhere for appendicitis, intestinal obstruction and ventral hernia, and presented a small intestinal fistula of four months' duration which developed following the last celiotomy. He had lost 40 pounds in weight during his illness. The wound was treated conservatively for several weeks when it was finally decided to close it surgically. This was done April 5, 1939, it required resection of much diseased small intestine on either side of the fistula but was successful. Preparatory to operation he was put on "nothing by mouth" and given intravenous injections of glucose, Ringer's solution and amino-acids, the amounts as indicated in the legend under Figure 3, vitamins C₁ and B₁ were also injected. It is interesting to note that during the period of gastro-intestinal rest the flow of intestinal contents from the fistula was active, the total nitrogen from this source varying between 0.2 and 0.9 Gm per 24 hours. This patient had two reactions during the injection of the amino-acids but in each case it was associated with a rapid rate of flow and was transient. The serum protein was 6.5 Gm per cent, albumin 4.2 Gm per cent. Following his discharge from the hospital the patient regained his loss of weight and has remained well.

Case 4—Hosp No 81491 J B, white, male, age 37, was admitted, October 20, 1939, to Barnes Hospital. He had become ill three months before with severe diarrhea and cramps which resulted in a 51 pound weight loss. On admission, he was emaciated and miserable, in spite of various oral regimens he continued to have three to ten stools a day and much abdominal pain. His serum protein remained low, 5.1 Gm per cent, albumin 3.0 Gm per cent. A diagnosis of regional ileitis was made, largely with the aid of a gastro-intestinal roentgenologic series, and operation was advised. This was carried out several months later, after he had gained 30 pounds in weight and had a normal serum protein. The lesion at operation proved to be characteristic of regional ileitis. On November 15, 1939, a period of intravenous alimentation was started, nothing was taken by mouth but cracked ice. The metabolic findings are recorded in Figure 4. The clinical response was pronounced, his pain disappeared, stools ceased, abdominal distention diminished, and general well-being improved remarkably. On the twelfth day of the experiment he was started on glucose and amino-acids by mouth, without any return of symp-

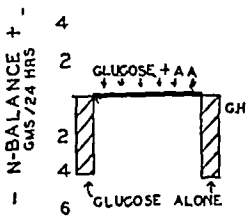


FIG 3

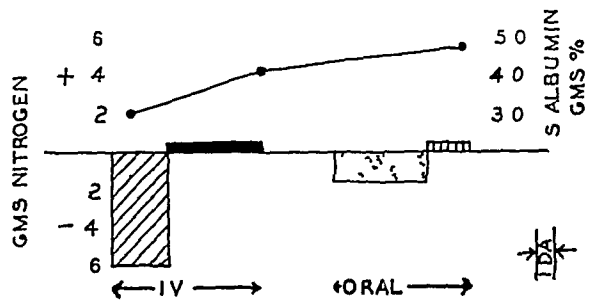


FIG 4

FIG 3—Case 3 and FIG 4—Case 4 These charts represent two preoperative cases (see Case Reports). Note in both, the achievement of positive nitrogen balance during the periods in which hydrolyzed casein was added to the intravenous glucose (represented in solid black). In Case 3 on the first and sixth days (represented by the cross hatched columns), 3,000 cc of 10 per cent glucose was injected. On the second to fifth days, 50 Gm of amino acids (6.0 Gm of N) was added daily. In Case 4, on the first three days (represented by the cross hatched columns), 3,000 cc of 10 per cent glucose was injected daily during the following five days, 60 Gm (7.2 Gm N) of amino acids was added. (The data on the ninth tenth and eleventh days are omitted because of difficulties with the intravenous flow and loss of specimens.) Note the negative nitrogen balance during the next five days (represented by the dotted column) when the same amount of glucose and amino acids was taken orally, this suggests the superiority of intravenous over oral administration. During the final two days the dose of amino acids was increased to 80 Gm (9.6 Gm N) whereupon nitrogen balance was achieved. Note also in this case the increase in serum albumin from 3.0 to 4.6 Gm per cent. The serum globulin remained unchanged at 2.1 Gm per cent as did the red cell count.

toms, and later was gradually put on a regular diet, upon this regimen he gained 30 pounds before being operated upon. It is of interest to note the increase in serum protein in this patient from 5.1 Gm per cent, on November 15, 1939, to 6.7 Gm per cent, three weeks later, the increase was all in the albumin fraction. No reactions whatever occurred during the intravenous therapy in this patient. His sense of hunger was definitely satisfied during the days in which he was receiving the amino-acids in contrast to its presence while receiving glucose alone. The metabolic studies in this patient were carried out with the cooperation of Dr Cyril MacBryde to whom I am indebted for the data obtained.

Case 5—Hosp No D-10914 B P, Negro, male, age 46, was admitted, February 8, 1940, to the Homer Phillips Hospital. He was operated upon soon after admission for a perforated peptic ulcer, which was found on the posterior surface of the pylorus, and was closed. The lesion had been present for over 24 hours, and a definite peritonitis was present. Intravenous glucose and Ringer's solution were given for five days, during this time his clinical course was stormy and, as can be seen in Figure 5, a large amount of nitrogen appeared in the urine. On the sixth day, amino-acids were added to the glucose and continued for 11 days. The sudden improvement in the general condition of the patient was striking and coincided with the addition of the amino-acids. Of interest, too, was the increase in the serum albumin and globulin, the

total serum protein changing from 6.11 Gm per cent on February 10 to 7.4 Gm per cent on February 27. That this change was not due to a concentration of the blood (decrease in plasma volume) was shown by the fact that the red cell count remained unchanged.

Case 6—Hosp No D-12080 S W, Negro, female, age 29, was admitted, March 14, 1940, to the Homer Phillips Hospital, and operated upon soon afterward for a strangulated umbilical hernia. The involved small intestine was gangrenous and a resection was carried out. During the first four postoperative days she received glucose and Ringer's solution alone, to which was added, during the next four days, 80 Gm of hydrolyzed casein. Thereafter she was started on fluids by mouth and finally a regular diet. The patient weighed but 50 Kg, so that the amount of amino-acids she received was almost 2 Gm per Kg. The clinical course was stormy for the first few days but improved remarkably with the onset of amino-acid injections. This was also evident, objectively, by a diminution of distention and the passage of gas and stool. It is important to note here, as in Case 5, the large urinary output of nitrogen in the postoperative period in spite of the administration of a large amount (1,600 calories) of glucose (Fig 6). Laboratory tests were otherwise not notable, the serum protein was normal.

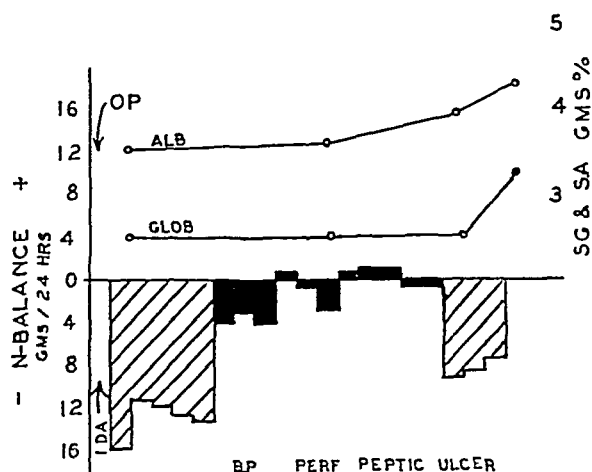


FIG 5

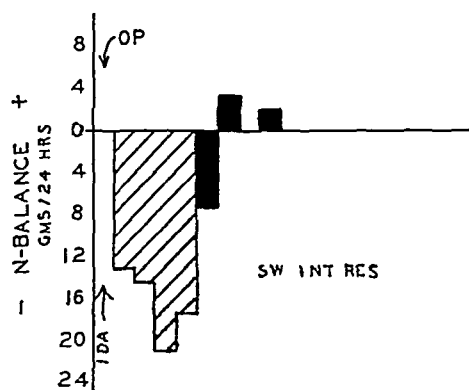


FIG 6

FIG 5—Case 5, and FIG 6—Case 6. These charts represent two postoperative cases (see Case Reports). Note the large output of nitrogen (12 to 20 Gm per day) in both in spite of the daily injection of 4,000 cc of 10 per cent glucose (represented by the cross hatched columns). The columns in solid black represent the addition of 80 Gm (9.6 Gm N) of 92-Z to the glucose, note that nitrogen balance was achieved on several but not on all of these days. Note, too, the increase in serum albumin and globulin in Case 5.

Case 7—Hosp No D-10954 J H, Negro, male, age 73, was admitted, February 9, 1940, to the Homer Phillips Hospital. He was operated upon soon afterward and a large volvulus of the sigmoid was untwisted, replaced in the abdomen and the wound closed. Recovery was uneventful, particularly after the third day, coincident with the addition of hydrolyzed casein, of which he received 80 Gm per day for 13 days together with 4,000 cc of 10 per cent glucose and Ringer's solution. The period of intravenous therapy was especially long because of persistent distention which finally subsided with the passage of normal stools. Note the large output of urinary nitrogen in this case (Fig 7). The laboratory data were not unusual. The serum protein showed no striking change varying between a low of 5.85 Gm per cent to 6.85 Gm per cent. On the last day of his intravenous regimen it was 6.66 Gm per cent, albumin 3.96 Gm per cent.

Case 8—Hosp No D-10336 A T, Negro, male, age 47, was admitted, January 22, 1940, to Homer Phillips Hospital. He had had a right lower quadrant mass of two weeks' duration, this was diagnosed as an appendiceal abscess and conservative therapy instituted. Because of increasing symptoms of extension he was operated upon five days later and a large spreading appendiceal abscess opened and drained. For the first four

postoperative days his course was quite stormy and repeated injections of caffeine were administered. Severe abdominal distention developed, the pulse was rapid, respirations labored. On the fifth postoperative day, amino-acids were added to the intravenous glucose, which resulted in a startling improvement, which continued thereafter. There was but one reaction during the course of the amino-acid therapy, consisting of a severe chill, unaccompanied, however, by any rise in temperature. The laboratory data were not significant. The serum protein four days after operation was 5.7 Gm per cent, albumin 3.6 Gm per cent, eight days later it rose to 6.7 Gm per cent, albumin 3.8 Gm per cent. There was no change in the red cell count. The metabolic data are represented in Figure 8, and show the high urinary output of nitrogen indicative of extensive "toxic destruction of protein."

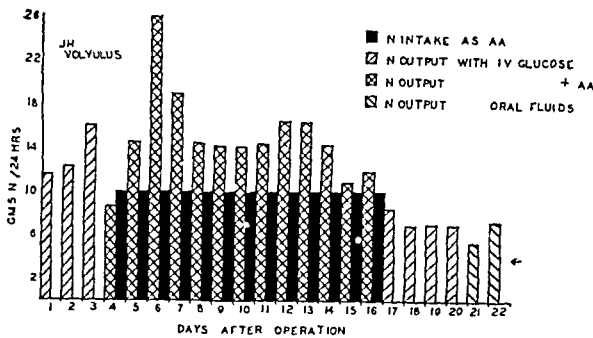


FIG 7

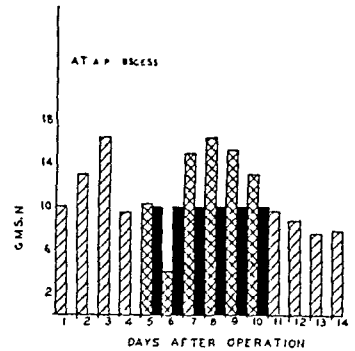


FIG 8

FIG 7 - Case 7 and FIG 8 - Case 8. The above charts represent two postoperative cases (see Case Reports). Note in both the large output of nitrogen in the urine (10 to 26 Gm per day). The arrow in Figure 7 indicates what is about the normal output (5 Gm). In both cases 4,000 cc of 10 per cent glucose was administered each day; the amount of hydrolyzed casein was 80 Gm (9.6 Gm N). Note that nitrogen balance was only occasionally achieved at this level of intake. (The low output in Case 8 on the sixth day was due to loss of a specimen.)

There was no difficulty in achieving nitrogen balance in patients with low or moderate nitrogen excretion even when but 6.0 Gm of nitrogen were injected per day (Figs 1, 2, 3 and 4). As observed previously,³ most fasting patients excrete about 4 to 5 Gm of nitrogen a day when sufficient glucose is injected to meet caloric needs. Many of the cases described herein, however, showed a large output of urinary nitrogen particularly following operations, amounting to as much as 26 Gm per day, in these a positive nitrogen balance was, therefore not achieved with regularity at the maximum intake of 9.6 Gm of nitrogen per day (Figs 5, 6, 7 and 8). Doubtless, with larger injections this could have been achieved. Nevertheless, favorable clinical effects were observed in several of these postoperative patients as soon as amino-acids were added to the intravenous glucose. This was particularly true in Cases 5, 6 and 8, which exhibited the largest output of nitrogen (see Case Reports).

In Cases 4 and 5, and less so in Case 8 definite evidence of serum protein regeneration was observed during the period of treatment. These observations are not decisive because the hypoproteinememia was not particularly severe. Indeed, few of the patients in the present series exhibited this defect to a significant degree.

COMMENT—From the findings reported herein, the inference seems justified that a mixture of amino-acids prepared by the enzymatic hydrolysis

of casein, when injected intravenously, is retained and, presumably, utilized by the body, sometimes even in a demonstrable increase in serum protein. Although few of the patients studied showed significant hypoproteinemia, of those that did two, possibly three, exhibited definite increases in serum protein and albumin while under treatment (Cases 4, 5 and 8). In other patients the therapy may have prevented a fall in serum protein, such a fall is a not infrequent experience in severely sick patients after operation. No such fall occurred in any of the patients receiving amino-acids. Although the present observations permit no dogmatic inferences as to the effect of intravenous amino-acids on serum protein regeneration, the achievement of positive nitrogen balance as well as the clinical improvement noted in many instances points to the beneficial therapeutic results of nitrogenous nourishment administered intravenously in this way. On the other side of the ledger are the difficulties encountered, the most serious being the occasional reactions observed. These reactions, I believe, are not an inevitable part of the procedure but are due to factors which may even now have been overcome by newer methods of preparation and administration of the enzymatic hydrolysate. With the achievement of a constantly uniform product, the use of amino-acids as a method of parenteral replacement of protein will undoubtedly have widespread application. While this use may not solve the fundamental problem of serum protein regeneration, I believe that, with all other protein needs met with amino-acids, a relatively small amount of blood, when necessary, will permit restoration of serum protein which can then be maintained for a sufficient length of time to permit normal relations to become established. The purpose of most parenteral alimentation, in surgery at least, is to clear temporary hurdles, by bringing patients into a more normal preoperative nutritional state, by breaking into a vicious circle induced by nutritional edema, and by permitting temporary gastro-intestinal rest, intravenous alimentation finds its most clear-cut indications. In this field the addition of nitrogenous nourishment should fill a long felt want.

✓An incidental finding in the present study concerns the tremendous output of urinary nitrogen in many patients during the postoperative period (Figs 5, 6, 7 and 8). It is of considerable interest and importance to note the magnitude of this loss, thus in Case 7, on the fourth day, 26 Gm. of nitrogen were excreted, which is equivalent to the loss of almost two pounds of muscle tissue a day. These losses were due to the disease itself and occurred in spite of the fact that each day 1,600 calories, as glucose, were injected, thus sparing protein as far as their use for caloric needs are concerned. Evidence of such "toxic destruction of protein" has been observed in a severe burn by Lucido,⁹ in postoperative patients, by Touw,¹⁰ and in patients following extensive trauma by Cuthbertson.¹¹ Its significance in the production of symptoms is suggested by the beneficial effects observed in several patients after much of the nitrogen loss was met by the addition of amino-acids to the intravenous glucose. These findings would seem to add a definite indication for such treatment in the postoperative care of very sick patients.

SUMMARY

(1) In 35 adults a solution containing glucose, amino-acids and electrolyte was injected intravenously as the *sole* source of alimentation, with the particular purpose of parenteral protein replacement. The amino-acids consisted of a mixture obtained by the enzymatic hydrolysis of casein. The maximum amount of nitrogen administered was 9.6 Gm per day, the calories, 1,600.

(2) Evidence of utilization was shown by (a) The achievement of nitrogen balance, (b) increases in serum protein concentration, and (c) clinical improvement, particularly after serious operations.

(3) Large amounts of urinary nitrogen were excreted by many patients after serious operations, indicative of "toxic destruction of protein." The clinical improvement during treatment seemed to be associated with the partial or complete replacement of this loss of nitrogen by the intravenously administered amino-acids.

(4) Certain difficulties in the intravenous injection of the amino-acid mixture are described and discussed. These are being rapidly solved by newer methods of preparation of the amino-acid mixture and of the solutions made therewith.*

REFERENCES

- ¹ Rose, W. C. The Significance of the Amino-acids in Nutrition. The Harvey Lectures, 30, 49-63 (see p. 64), 1934-35.
- ² Henrique, V., and Andersen, A. C. Über parenterale Ernährung durch intravenöse Injektion. Ztschr. f. physiol. Chem., 88, 357, 1913.
- ³ Elman, R., and Weiner, D. O. Intravenous Alimentation. J. A. M. A., 112, 716, 1939.
- ⁴ Cox, W. M., Jr., and Mueller, N. J. Nitrogen Retention on Casein Digests. Proc. Soc. Exper. Biol. and Med., 42, 658, 1939.
- ⁵ Elman, R. Serum-Albumin Regeneration Following Intravenous Amino-acids (Hydrolyzed Casein) in Hypoproteinemia Produced by Severe Hemorrhage. Proc. Soc. Exper. Biol. and Med., 43, 14, 1940.
- ⁶ Shohl, A. F., Butler, A. M., Blackfan, K. D., and MacLachlan, E. Nitrogen Metabolism During Oral and Parenteral Administration of the Amino-acids of Hydrolyzed Casein. Jour. Pediat., 15, 469, 1939.
- ⁷ Farr, L. E., and MacFayden, D. A. Amino-acid Nitrogen in Urine of Children with Nephrotic Syndrome Following Intravenous Amino-acids. Proc. Soc. Exper. Biol. and Med., 42, 444, 1939.
- ⁸ Farr, L. E. Personal communication.
- ⁹ Lucido, J. Metabolic and Blood Chemical Changes in a Severe Burn. ANNALS OF SURGERY, 111, 640, 1940.
- ¹⁰ Touw, J. F. Harnstoffspiegel im Blut nach Operation. Ztschr. f. Klin. Med., 130, 497, 1936.
- ¹¹ Cuthbertson, D. P. Observations in the Disturbance of Metabolism Produced by Injury to the Limbs. Quart. Jour. Med., 1, 233, 1932.

* At the present time a 10% glucose 2½% amino-acid solution is prepared in the cold, immediately passed through a large capacity Berkfeld filter to remove pyrogens and autoclaved at once in 1000 cc flasks for 30 minutes at 5 lbs pressure. Thus far no febrile reactions have been observed with solutions prepared according to this much more simple method.

THE RELATION OF PROPER PREPARATION OF SOLUTIONS FOR INTRAVENOUS THERAPY TO FEBRILE REACTIONS*

CARL W. WALTER, M.D.

BOSTON, MASS.

FROM THE LABORATORY FOR SURGICAL RESEARCH, HARVARD MEDICAL SCHOOL, AND THE SURGICAL CLINIC OF THE PETER BENT BRIGHAM HOSPITAL, BOSTON, MASS.

WIDESPREAD DEMAND for an inexpensive source of safe parenteral fluids has resulted from the recognition of the importance of maintaining a positive water balance as an adjuvant in hastening convalescence. Many hospitals prepare their own solutions in an endeavor to make adequate parenteral therapy economically feasible for all their patients. Other hospitals would like to reduce the cost of providing such solutions, but are loath to undertake the preparation of parenteral solutions because they fear the occurrence of untoward allergic or febrile reactions.

During the period between 1933 and 1936, a technic was developed at the Peter Bent Brigham Hospital which enables hospitals to prepare parenteral fluids safely and inexpensively. Since then, 250 hospitals have had experience with this technic. As a result, the technic and apparatus have become sufficiently standardized to warrant demonstration before this society.

There are but two requisites for a safe supply of parenteral fluid: A source of pure raw materials, and centralized responsibility for cleanliness in preparation of the solutions and apparatus. Any hospital in which major surgery is performed has the necessary sterilizing equipment and the trained personnel to whom such responsibility can be delegated safely.

Clinicians persist in adhering to numerous conjectures regarding the cause of intravenous reactions despite convincing laboratory and clinical evidence explaining the etiology of such reactions. In 1911, it was shown that chemically pure distilled water would not cause reactions when injected intravenously,²⁰ that such water was readily contaminated and made pyrogenic by air-borne bacteria,⁶ and that Berkefeld filtration did not remove the offending substance.⁴

More recently (1923), such pyrogens were demonstrated to be filterable, thermostable exotoxins removable by distillation in a still designed to prevent entrainment. If kept sterile, pyrogen-free water remained so.^{11, 12, 13, 14, 15}

Subsequently, it was found that pyrogenic water could be rendered innocuous by heating it to 284° F (38 p.s.i. gauge) for 30 minutes.¹ Adsorptive filtration was also found to be effective in removing the objectionable proteins.²

The application of these factors resulted in the rapid development of commercial sources of reliable parenteral fluids and in numerous demonstrations that hospital-made solutions are safe, economical, and practical.^{5, 7, 8, 9} Ac-

* Read before the American Surgical Association, St. Louis, Mo., May 1, 2, 3, 1940.

cordingly, rational parenteral therapy should be available in modern hospitals, and the volume, velocity, temperature, and composition of the injection may be left entirely to the discretion of the clinician. The intravenous injection of chemically pure, sterile solutions will not cause untoward reactions.

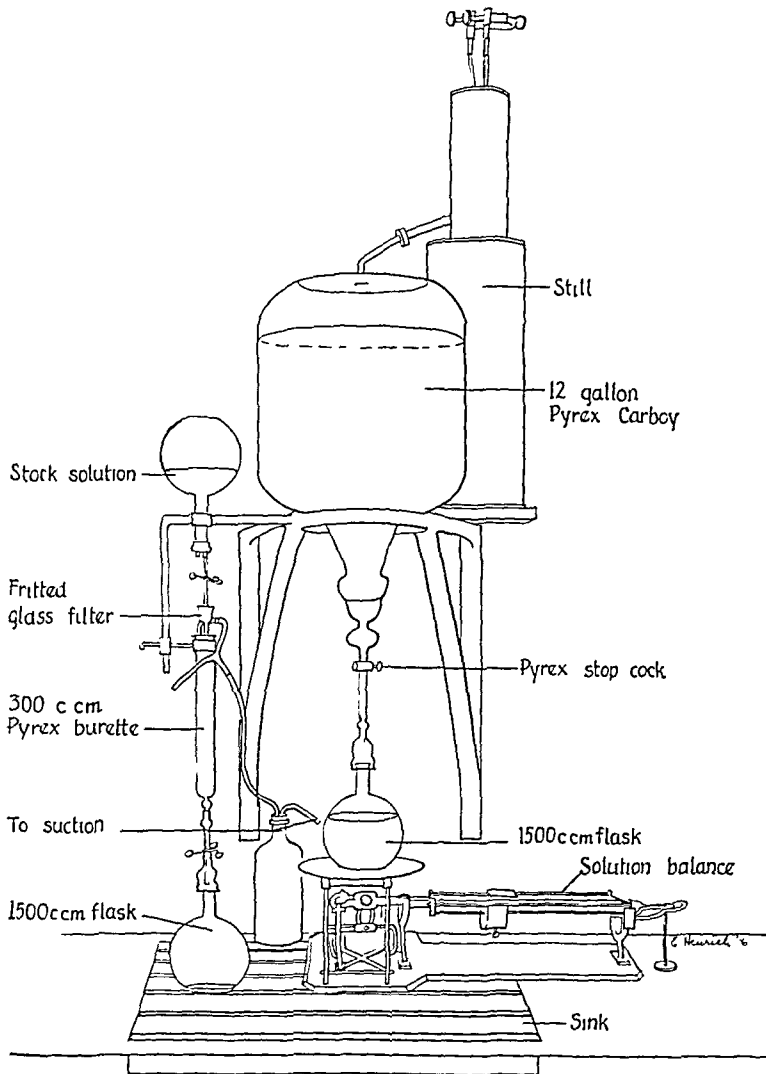


FIG. 1—Arrangement of apparatus to facilitate the preparation of parenteral solutions. Distilled water for immediate use only is collected in an inverted pyrex carboy. The solutions are made by diluting & filtered concentrate gravimetrically.

Distilled Water—Singly distilled water is sufficiently pure for intravenous use provided several precautions are taken to prevent pollution of the distillate. First, intelligent operation and maintenance of the still are essential.

Second, chemically pure distilled water cannot be stored unless it is hermetically sealed in sterile containers, hence, distilled water must be collected in a storage tank just large enough to contain a working supply. An inverted pyrex carboy (Fig. 1) fitted with a glass stopcock is best because such a container can be drained dry and has no gauge glasses, faucets, or valleys where

residual water may pool and support bacterial growth which pollutes subsequent collections of distillate. Such carboys should be drained as soon as there is no immediate use for distilled water.

Third, the purity of the water must be determined frequently. Since pure water is a comparatively poor conductor of electricity, its specific conductance is an excellent measure of its purity. The distillate from a well-designed, properly operated still should have a maximum conductivity of 2×10^{-6} mhos at 20°C . One part per million of chloride ion will increase the conductivity of distilled water about 50 per cent. The presence of electrolytes in freshly distilled water indicates contamination with tap water either by entrapment or by leakage from a faulty condenser. Then it may be assumed that the water has also been contaminated by pyrogenic substances which accompanied the electrolytes. Therefore, the efficiency of a still can be checked quickly and accurately by determining the specific resistance of the distillate by means of a 1,000 cycle Wheatstone bridge. Some stills produce impure water sporadically and should be equipped so that the purity of the distillate is checked continuously.

Biologic methods must be employed to identify actual pyrogen content. The most readily applicable test is that of injecting 10 cc of the questionable solution into the ear vein of a rabbit and determining the rectal temperature at hourly intervals for three or four hours. The rabbit's normal temperature ranges from 101.2° to 103°F under standardized conditions. The febrile reaction which results from the injection of pyrogen raises this to 105° – 107° .^{11, 14}

Chemicals—Although the United States Pharmacopeia does not specify dextrose suitable for intravenous use, U.S.P. XI or C.P. anhydrous grades of chemicals are usually satisfactory. Sodium chloride and dextrose are purchased most economically in drums of 25 and 200 pounds respectively. Careless transference of the chemicals must be avoided and any which touches the hands or drops upon the balance or table top should be discarded rather than be returned to the bulk container.

There is an advantage other than economy in buying the chemicals in bulk because, once the purity of any lot has been established, a supply of known quality is available. Dextrose may contain protein split products and/or various acid dehydration products of dextrose formed by side reactions during the manufacture of dextrose.

The protein contaminant is present in the form of amino-acid-carbohydrate condensations or polypeptide intracrystalline occlusions. These compounds undergo heat denaturation during sterilization and form white, flocculent precipitates in the final solutions. They can be detected by denaturing them

* Conductance, the reciprocal of resistance, is measured by the ratio of the current flowing through a conductor to the difference of potential between its ends. The practical unit of conductance, the mho, is the conductance of a body through which one ampere of current flows when the potential difference is one volt. Conductivity is measured by the quantity of electricity transferred across unit area per unit gradient.

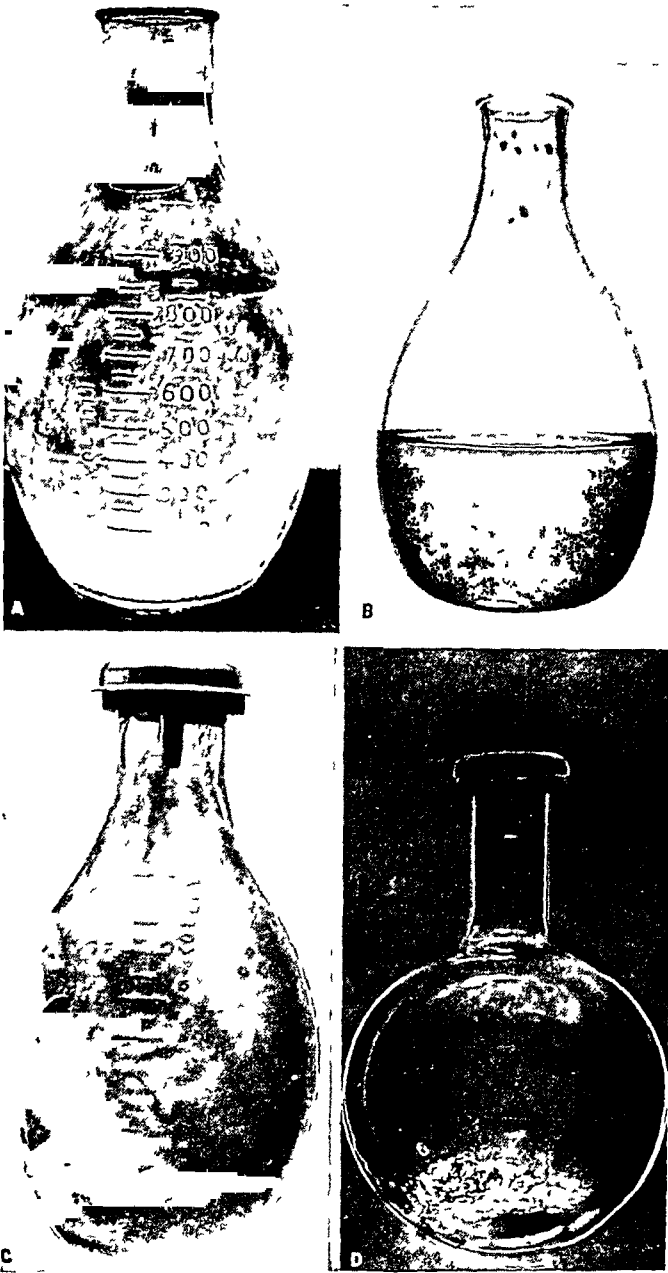


FIG 2—(A) Clean glassware is free of this white opalescent film of insoluble alkaline earth soaps formed by the interaction of soap and/or detergents and the calcium or magnesium salts which are found in tap water or soil. A film of distilled water remains spread over the surface of clean glass as the water is poured off. Grease or other soil causes this film to 'break' into the numerous droplets illustrated (B). Bacterial growth in residual blood (C) or solution (D) left in apparatus may produce pyrogen. Unless thoroughly cleaned such apparatus may contaminate pure solution with pyrogen.

mechanically by passing 50 per cent dextrose through the clarifying bowl of a Sharples centrifuge or forcing it through an atomizing jet. In either case the impure solution becomes opalescent and dirty white or yellow curds separate out on standing. Such polypeptides can be removed by adsorptive filtration or ultrafiltration.

The dehydration products are chiefly hydroxymethyl furfural and levulinic acid²¹. The former is colorless, but, on aging, it degrades to levulinic acid, a dark brown compound. This conversion occurs rapidly in hot aqueous solutions and accounts for the yellow color (often mistaken for caramelization).

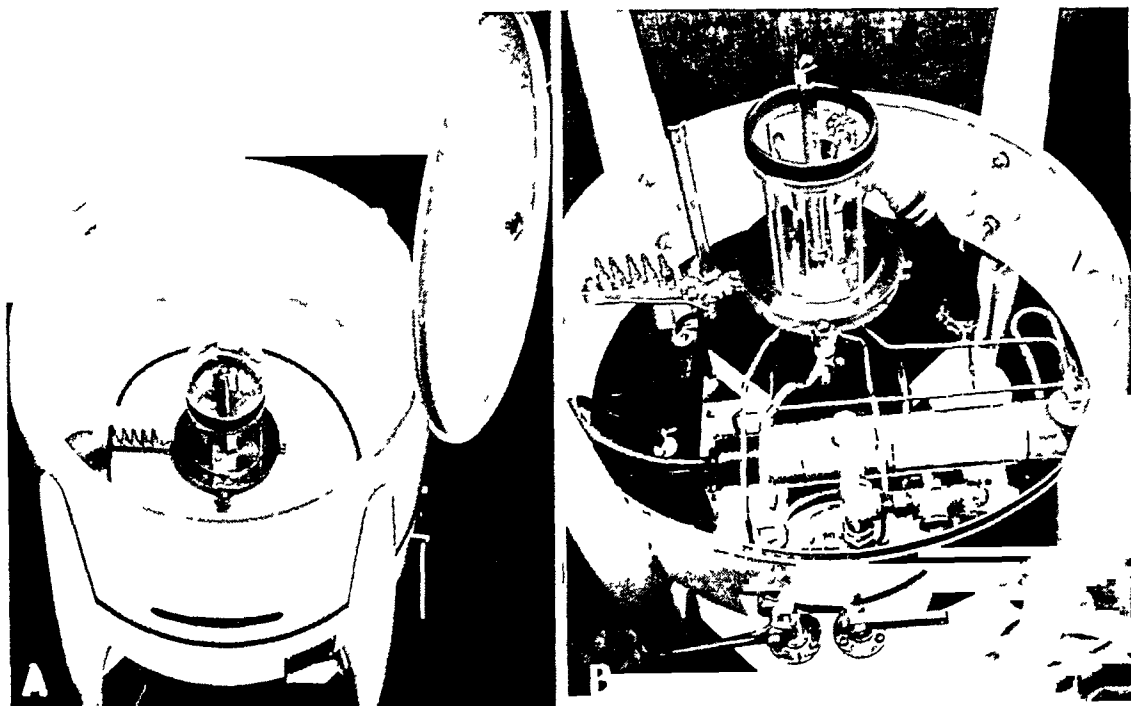


FIG 3—A mechanical washer (A) most readily cleans the inner surface of glassware, tubing, and needles by scouring them with hot detergent solution. The washer uses the detergent solution repeatedly, automatically filtering, reheating, and pumping it through suitable jets under high pressure. The flask washer is shown at the upper center (B), the needle and tubing nipples can be seen at the left.

developed during sterilization of some dextrose solutions.

The acceptance of any particular lot of chemical also depends upon the quantity of particulate matter contaminating it. Excessive dust not only clogs the filters quickly, but is evidence of careless handling prior to packaging. The finding of a shoelace tip or a dried insect indicates contamination of a degree likely to introduce foreign proteins into the chemicals. Dirty chemicals must be rejected.

Glassware—Pyrex glassware is the most satisfactory, not only because of its high resistance to mechanical and thermal shock, but because its stable annealed surface resists hydrolysis by the solutions. The alkaline film formed at the glass-liquid interface of a soft glass flask may cause polymerization of the dextrose during sterilization.

To be chemically clean, glassware must be freed of the initial soil as well as of insoluble deposits (Fig 2 A) resulting from the interaction of washing agents (soaps and detergents) and water or soil containing more than traces

of alkaline earths^{3 10} (Ca and Mg) Clean glass should show no "water breaks" (Fig 2 B) in the film of distilled water left after the final rinsing, and it should be crystal clear when dry



FIG 4—The containers are rinsed by inverting them over a spray of freshly distilled water. The stainless steel sprayer illustrated conserves distilled water by shutting it off when not in use and also by metering the amount used. When the flask is first inverted over the spray the cup at the bottom is empty. The rinse water collects in this cup giving an idea of the amount used as well as rinsing the outside of the neck. One hundred cubic centimeters of distilled water (enough to fill the cup twice) suffices to remove all the alkali.

Dried blood (Fig 2 C) and closely adherent bacterial growths (Fig 2 D) are the usual types of soil encountered. Dried fungi are particularly difficult to remove. They may be invisible until hydrolyzed during sterilization, at which time they swell and become opaque and may be mistaken for wisps of cotton floating in the solution. Because glassware is often used in the

laboratory or utility room, residues of feces, urine, pus, and transudates are often encountered. The most tenacious soil is a greasy film which accumulates when the glassware is used repeatedly without adequate cleansing.

The containers are most readily cleansed in a mechanical washer (Fig 3) which forces hot detergent solution* through jets under sufficient pressure to scour the inner surface. This mechanical action augments the effectiveness of a good detergent and cleanses in 15 or 20 seconds. The glassware is rinsed thoroughly with freshly distilled water by inverting it over a jet (Fig 4) which sprays distilled water on the entire inner surface. Usually 100 cc of water suffice to rinse away all the alkali. The container is then inverted to drain.

The stainless-steel stoppers and rubber bushings are cleaned by scrubbing them thoroughly with hot detergent solution and rinsing them in freshly distilled water.

Filters—Fritted glass or porcelain filters are readily cleaned by immersing them in a hot solution (175° F) containing ½ per cent each of sodium nitrite and sodium chlorate in concentrated sulphuric acid. The acid is rinsed from the porous disk by running distilled water through the filter in the reverse direction until the rinsings are neutral to litmus paper or until the conductivity of the rinsings approaches that of the original distilled water.

Equipment—The equipment chosen for the preparation of parenteral fluids should provide for easy sterilization, safe storage under hermetic seal, and ready administration from the original container^{16, 17, 18, 19}. Such apparatus (Fig 5) consists of a container which can be hermetically sealed by means of a rubber bushing and stainless-steel stopper. The elements of the seal are assembled prior to sterilization so that possible contamination during sealing is avoided. The contents of the flask can be infused by substituting a special "vent tube" through which the fluid leaves the inverted container by gravity, for the stainless-steel stopper.

Container—The graduated container is mold-blown of thick Pyrex glass in a shape designed to withstand the water-hammer which results when fluids under high vacuum are jarred. Its wide mouth and short neck facilitate cleaning. The contour of the mouth and lip is such that the rubber bushing is held securely in place.

The rubber bushing is molded of nontoxic, heat-resistant rubber which retains its resiliency after repeated sterilization and does not become tacky and stick to either the container or the stopper. It is shaped to cling firmly to the mouth of the container. The frustum of the bushing fits snugly against the inwardly tapering portion of the neck of the container to prevent the bushing from being pushed inward during sealing, or from being drawn into the flask as the vacuum is formed. The elastic periphery of the skirt clings to the lip of the flask, holding the bushing in position when the stopper is withdrawn or when the container is inverted in the dispensing position.

* Any commercial dishwashing compound which leaves the glass crystal clear on drying is satisfactory.

The stopper is fabricated of a corrosion-resisting, stainless-steel to withstand the attack of saline solutions, as well as to resist tarnish from an atmosphere of air or steam. The mushroom-shaped stopper is essentially a rugged cap, which covers and protects the rubber bushing, and a stem which actually provides the closure. A longitudinal channel cut into the lower third of the stem provides an adequate vent for the escape of air and steam during

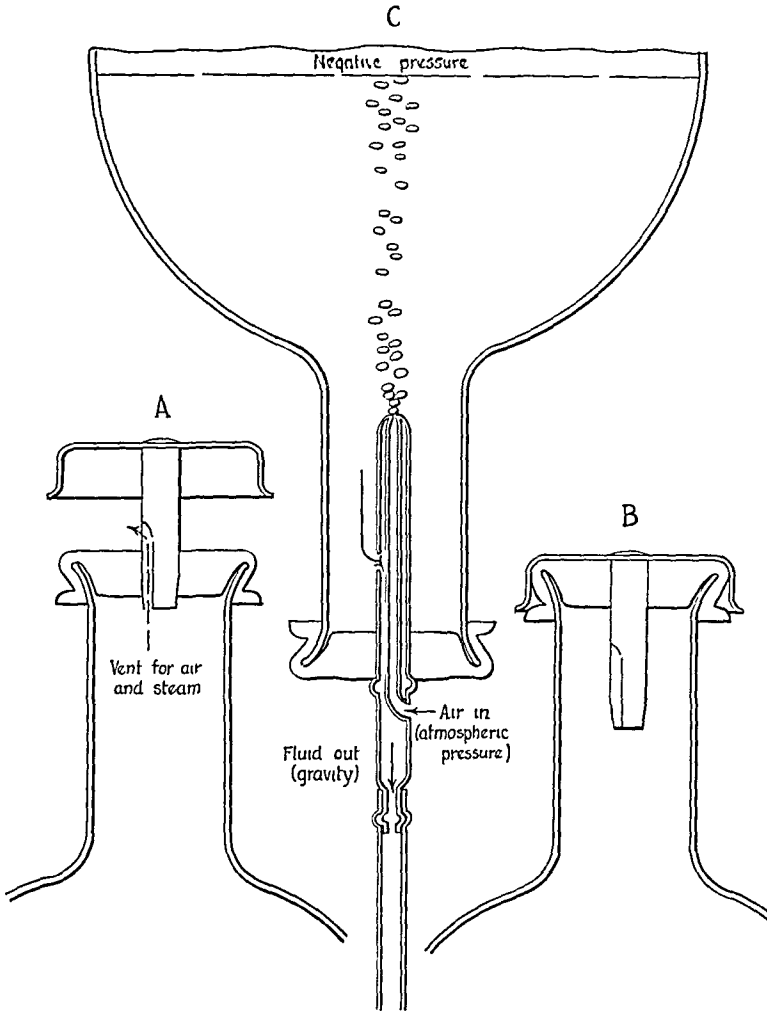


FIG. 4.—Flask preparation sterilization safe storage and ready administration are provided in this simple container. (A) The channel in the steel stopper provides for the escape of air and steam during sterilization. (B) A vacuum seal is produced by inserting the stopper into the bushing and permitting the flask to cool. (C) Air enters the capillary orifice in the vent tube to relieve negative pressure within the inverted flask.

sterilization (Fig 5 A). A rush of steam through this channel, due to the sudden ebullition of vapor following faulty venting of a sterilizer, serves to warn the alert operator that the solutions have been spoiled. On removal from the sterilizer, the stopper is locked into the bushing so that the solid portion of the stem forms a hermetic seal with the bushing (Fig 5 B). Precipitation of the water vapor and contraction of the fluid during cooling produces a high degree of vacuum (29 inches Hg.) which aids in maintaining

the seal. The water-hammer click which is obtained by jarring a sealed flask gives evidence that the container has been properly sterilized and sealed.

The fluid is dispensed from the original container by substituting the hard glass vent tube for the steel stopper (Fig. 5 C). This tube comprises a pair of concentric glass tubes, the external diameter of which corresponds to the aperture in the bushing, so that it makes a water-tight fit with the latter. Two circumferential ribs or beads serve to position the tube firmly in relation to the bushing. Fluid enters the annulus of the vent tube through a small orifice just above the inner bead and leaves through the tubing nipple at the outer end of the vent tube, permitting free gravity flow from the inverted flask.

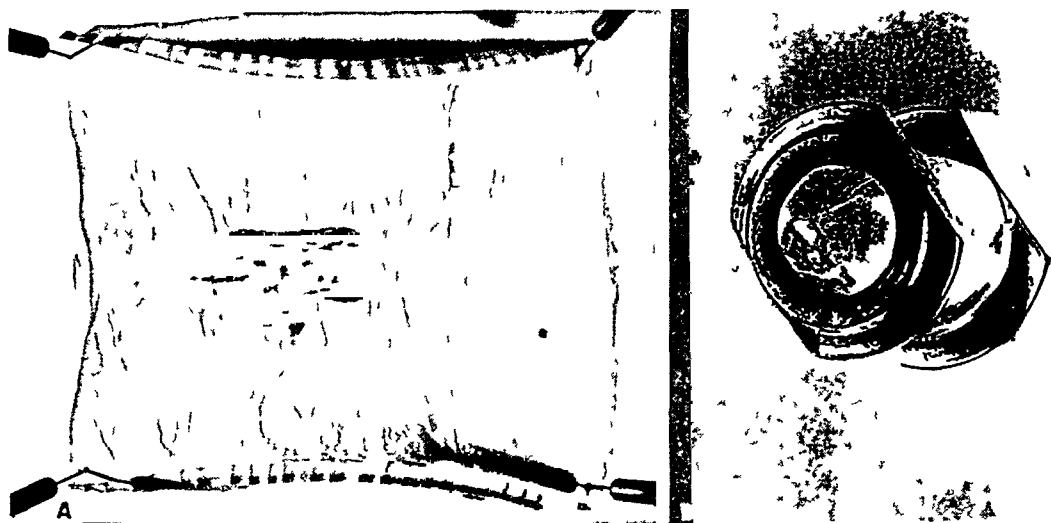


FIG. 6—Pits, wrinkles, and mold marks on the inner surface of rubber tubing catch blood or hold residual solution where bacteria may grow. Tubing with a smooth inner surface can be cleaned readily, whereas the bits of the dried blood clot (A) or colonies of bacteria lodge tenaciously in the hollows of the rough surface. Bacterial growth in the lumen of the cannula or hub of a needle may contribute pyrogen. Even cursory inspection of the hub should have detected the clot illustrated (B). The cannulae must be reamed with a tightly fitting stilet to insure cleanliness.

Air is metered into the flask to overcome the increasing negative pressure caused by the escape of fluid. This is done by means of the inner tube which communicates with the atmosphere just below the outer bead and leads inwardly to a capillary orifice at the upper end of the vent tube. This capillary is small enough to prevent the fluid leaking through the air vent when the negative pressure is too low to support the static head of the fluid in the flask.

Rubber Tubing—In selecting rubber tubing for use in parenteral therapy, it is essential that the inner surface be free from pits, wrinkles, and mold marks, where blood and bacterial residues lodge and make cleaning difficult (Fig. 6). The surface of rubber exposed to the fluid can be decreased markedly by selecting a tubing of small inside diameter ($1/8$ inch). A small lumen also facilitates the expulsion of air from the system, since fluid tends to run through it as a solid column rather than to trickle down one side as in a gutter. Any nontoxic rubber can be used, but it is more economical to select a rubber compounded to insure maximum heat resistance. Tubing available at present will withstand 75 sterilizations before it loses its elasticity.

Preparation of Solutions—The avoidance of mass filtration and bulk dilution of solutions will be found convenient in most hospitals. The problems entailed in handling large quantities of fluid can be avoided by a technic which also limits potential spoilage due to improper mixing, faulty filtration, careless contamination or uncleanness, to individual flasks. Such technic is based upon the filtration of a relatively small proportion of the final solution in the form of a concentrate. This concentrate is then diluted with distilled water which should contain no particulate matter if properly distilled and collected. In the average hospital, the concentrate is filtered most advantageously into a large volumetric burette whence a suitable portion is measured into a container and distilled water added until the proper dilution by weight is made (Fig 1).

Five per cent dextrose solution is prepared from a fresh stock solution made by adding hot distilled water to 1,000 Gm of chemically pure dextrose, previously weighed out in a counterbalanced flask, until a net weight of 2,355 Gm has been reached. The flask is stoppered with a clean rubber stopper and shaken until solution is complete. This stock solution is then filtered through a fritted glass (17 G 5/3), porcelain filter (F G -450-10), or adsorptive filter (Seitz uhlenhuth 60 Mm germicide EK), with the aid of suction, directly into a pyrex burette. The filtrate should be crystal clear and colorless. The stock solution can be decolorized and clarified if necessary by adding 1 to 2 per cent activated charcoal (Norit*) prior to filtration. One hundred cubic centimeters of the filtrate are measured into a counterbalanced, pyrex container, and distilled water is added to a net weight of 1,066 Gm. A clean rubber bushing is fitted into the mouth of the flask its skirt is turned down, and the channeled stem of the steel stopper is partially inserted into the bushing. The solutions are sterilized immediately in an autoclave at 250° F (exhaust line temperature¹⁸) for 30 minutes. After sterilization the steam supply to the autoclave is shut off to permit the autoclave to cool to 200° F before it is opened. In this way, concentration of solution resulting from the ebullition of steam following sudden relief of pressure is avoided. As the flasks are removed from the autoclave, the steel stoppers are pushed in to complete the seal. The sterile, sealed solutions can be stored indefinitely without impairing their value as safe parenteral fluids.

Preparation of Intravenous Kits—The establishment of a source of chemically pure parenteral fluids is futile unless an equally safe supply of apparatus for its administration is constantly available. Bacterial growth in residual solution or blood in such equipment produces pyrogen which must be removed by adequate cleansing with pyrogen-free water. Chemical cleanliness of the inner wall of the vent tubes, rubber tubing, observation tubes, and needles is essential for safe, reactionless infusions.

The cleansing of such apparatus must be done immediately before sterili-

* Norit (decolorizing carbon—P1731), Research Laboratory, Eastman Kodak, Rochester, New York

zation, because bacteria are likely to grow in the moisture left in the apparatus to insure sterilization

The rubber tubing is cleaned by slipping one end over the nipple of the automatic washer (Fig 3) and flushing the lumen for one minute with detergent solution under pressure. Freshly distilled water is then run through the tubing for ten seconds to remove the detergent and leave the inner surface chemically clean. No attempt is made to dry the lumen of the tubing.

The small glass parts, vent tubes and observation tubes, can be cleaned rapidly by sucking hot detergent solution through them. This can be done

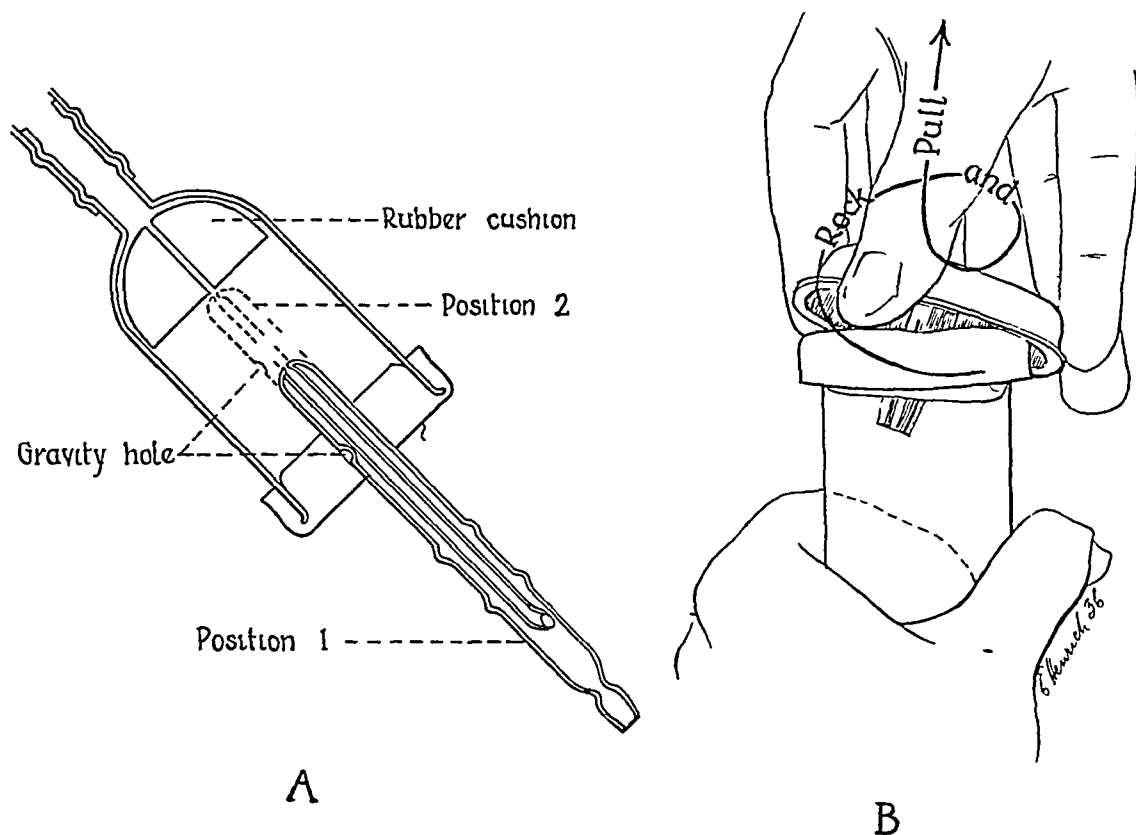


FIG 7—The pyrex vent tubes are easily cleaned by sucking hot detergent solution through them (A). In position 1, the gravity outlet is occluded while the air tube is rinsed, at 2, both passages are cleansed.

The stainless steel stopper is readily removed by a rocking, spiral motion (B).

most easily in the case of the pyrex vent tubes by using a special holder which permits positioning of the tube, so that the capillary vent and the fluid passage can be cleansed and rinsed separately (Fig 7 A).

Needles are cleaned by locking them on the Luer-lock needle adapters provided for the purpose in the mechanical washer and forcing hot detergent solution through them. They are rinsed with distilled water and inspected critically, not only for sharpness, but also for weakness which might cause unexpected breakage. This is done by holding the hub firmly while the tip is sprung through an arc. Those which have been weakened will snap off or bend at the junction of the hub and needle. Needles should not be sterilized with stilets in place because the electrolytic action set up between the stilet and the needle causes early corrosion and weakening.

The various elements of the infusion apparatus are reassembled without drying, and the equipment is arranged in a clean aluminum tray (Fig 8A). This tray is inserted into the sterilizing envelope, the inner flap of which is tucked beneath the pan and the outer flap securely pinned. The kits must be sterilized without delay. The residual water inside the rubber tubing is vaporized in the sterilizer and provides the moisture essential for sterilization. It is important to have the tubing moist because it is difficult to clear sufficient air from a length of dry coiled rubber to attain sterilizing conditions.

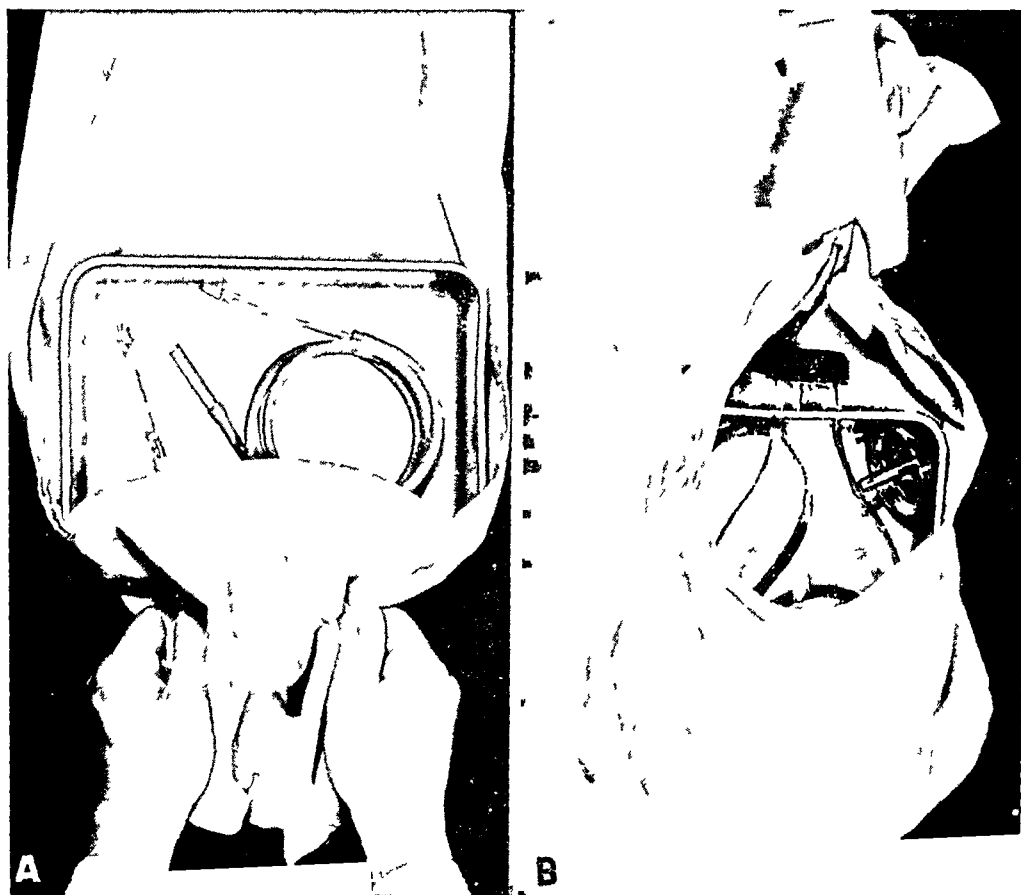


FIG 8—The arrangement of the elements of the infusion apparatus assembled in the sterilizing tray is illustrated (A). The tubing is coiled so that the vent tube is uppermost. The tray is easily extruded from the sterilizing envelope by forcing the sides of the envelope together. The envelope also serves as a convenient means of returning the apparatus to the supply room (B). The vent tube is removed from the bushing and put into the tray along with the needles and steel stopper. The bushing is left in place to prevent accidental chipping of the lip of the container.

Sterilization of Kits—The kits are packed into a dressing sterilizer so that the bottoms of the aluminum trays are in a vertical position. This permits the steam to displace the air and results in the rapid development of sterilizing temperatures. It is advantageous to sterilize them alone or with loosely wrapped rubber goods because little heat is required to bring the kits to sterilizing temperature. They should be sterilized for 30 minutes at 250° F (exhaust line temperature).

After sterilization the envelopes are dried by leaving the sterilizer door

ajar for 15 minutes while the steam pressure is maintained in the jacket. If the kits are stored with the trays inverted, there is little danger of contamination from dust and they can be kept until needed.

Administration—When an infusion is ordered, it is necessary to obtain only an intravenous kit and a container of the appropriate solution. The sterility of the solution is tested by striking the inverted flask sharply with the palm, driving it suddenly away from its liquid contents. The liquid subsequently strikes the flask again producing a metallic water-hammer click. This phenomenon indicates a vacuum of 29 inches of mercury—assurance that the flask was heated sufficiently to drive off the air prior to sealing, and that the hermetic seal has been maintained. The fluid is administered from the original container by removing the steel stopper by a spiral, rocking, twisting motion (Fig 7 B). An inrush of air, as this is done, is additional evidence that the flask has not been opened following sterilization.

The outer flap of the sterilizing envelope is loosened and the corners of the envelope are grasped and pushed together to extrude the aluminum tray from the envelope (Fig 8 A). This provides, simultaneously, a sterile field and a receptacle to catch the liquid when the air is being expelled from the rubber tubing.

The portion of rubber tubing stretched over the nipple of the pyrex vent tube is then grasped and the latter is “wiggled” into the hole in the rubber bushing until the groove between the shoulders of the vent tube is seated in the rubber bushing (Fig 5 A). This tube acts as a valve for the admission of air to overcome the negative pressure created in the container as the fluid leaves under the influence of gravity. Since the surface tension across the capillary orifice at the top of the valve is sufficiently great to support the column of water in the container, there should be no leakage of solution from the air vent once a negative pressure has been established in the flask. This is done conveniently by inverting the flask, hanging it in the splitting bracket, and permitting the solution to run through the rubber tubing into the aluminum pan before the needle is attached.

The needle is readily withdrawn from the hour-glass sterilizing tube by removing the cotton plug and inserting the ground-glass tip of the observation tube into the hub of the needle. The needle can be attached firmly enough to prevent dropping or contaminating it.

The rate of injection can be predetermined (within limits) by holding the needle level with the vein into which it is to be inserted and varying the pressure head by raising or lowering the flask. For all practical purposes either a 19 or 21 gauge needle will provide an ample range of flow. The infusion is now ready to start.

More fluid than is contained in one flask may be given by substituting a second flask as the first one is emptied. This is done by clamping off the rubber tube with a Hoffman clamp before removing the vent tube from the first flask. The vent tube is then inserted into the bushing of a fresh flask of solution, the container inverted, and the Hoffman clamp removed.

After the infusion has been completed, a small gauze sponge is held gently over the skin puncture and the needle is withdrawn. Pressure is maintained over the sponge for at least five minutes until the hole in the vein has sealed off. This precaution prevents extravasation of blood into the subcutaneous tissues with the subsequent unsightly discoloration of the overlying skin.

Return of Apparatus to the Central Supply Room—The infusion apparatus is removed from the split-ring bracket and placed in the aluminum pan, without being disassembled, along with the stainless-steel stopper, extra needles, and the hour-glass sterilizing tube. The pan is then inserted longitudinally into the sterilizing envelope (Fig 8 B) and returned to the central solution room. The long flap of the envelope serves as a handle so that five or six sets can be carried conveniently in one hand without danger of loss or breakage.

Thus, the preparation of safe parenteral solutions depends upon a clear understanding of the meaning of the term "chemically pure" and its differentiation from the word "sterile." The technic, here outlined, enables any hospital to prepare parenteral solutions at a cost which permits adequate therapy to be given all patients in whom it is indicated.

REFERENCES

- ¹ Banks, H M. Study of Hyperpyrexia Reaction Following Intravenous Therapy. *Am Jour Clin Path*, 4, 260, 1934.
- ² CoTui, McCloskey, K L, Schrift, M, and Yates, A L. A New Method of Preparing Infusion Fluids. *J A M A*, 109, 250, 1937.
- ³ Hall, G O, and Schwartz, C. Sanitary Value of Sodium Metaphosphate in Dishwashing. *Ind and Eng Chem*, 29, 421, 1937.
- ⁴ Hort, E C, and Penfold, W J. The Dangers of Saline Injections. *Brit Med Jour*, 2, 1589, 1911.
- ⁵ Meade, G M. Dollars Plus Safety. *Hospitals*, November, 1939.
- ⁶ Muller, P T. Über den Bakteriengehalt des in apotheken erhältlichen destillierten Wassers. *Munchen med Wchnschr*, 58, 2739, 1911.
- ⁷ Nelson, C M. The Cause of Chills Following Intravenous Therapy. *J A M A*, 112, 1303, 1939.
- ⁸ Rademaker, L. Cause and Elimination of Reactions after Intravenous Infusions. *ANNALS OF SURGERY*, 92, 195, 1930.
- ⁹ Rademaker, L. Reactions after Intravenous Infusions. Further Report on Their Elimination. *Surg, Gynec and Obstet*, 56, 956, 1933.
- ¹⁰ Schwartz, C, and Gilmore, B H. Sodium Metaphosphate in Mechanical Dishwashing. *Ind and Eng Chem*, 26, 998, 1934.
- ¹¹ Seibert, F B. Fever Producing Substance Found in Some Distilled Waters. *Am Jour Physiol*, 67, 90, 1923.
- ¹² Seibert, F B. Cause of Many Febrile Reactions Following Intravenous Injections. *Am Jour Physiol*, 71, 621, 1925.
- ¹³ Seibert, F B. Welche Substanzen erzeugen Fieber nach Intravenaesser Injektion? *Arch f exper Path u Pharmakol*, 121, 247, 1927.
- ¹⁴ Seibert, F B, and Mendel, L B. Temperature Variations in Rabbits. *Am Jour Physiol*, 67, 83, 1923.
- ¹⁵ Seibert, F B, and Mendel, L B. Protein Fevers, with Special Reference to Casein. *Am Jour Physiol*, 67, 105, 1923.
- ¹⁶ Walter, C W. Economical Intravenous Therapy. *J A M A*, 104, 1688, 1935.

- ¹⁷ Walter, C W Simplified Apparatus for the Administration of Parenteral Fluid
J A M A , 106, 1982, 1936
- ¹⁸ Walter, C W Preparation of Safe Intravenous Solutions Surg , Gynec and Obstet ,
63, 643, 1936
- ¹⁹ Walter, C W A Reliable Control for Steam Sterilization Surg , Gynec and
Obstet , 67, 526, 1938
- ²⁰ Wechselmann Neuere Erfahrungen ueber intravenoese Salvarsaninjektionen ohne
Reaktionserscheinungen Munch med Wchnschr , 58, 1510, 1911
- ²¹ Krno, J M Corn Products Sales Company, New York Personal communication,
May, 1940

Discussion—DR DALLAS B PHEMISTER (Chicago, Ill) Fluid and electrolyte need from local loss of plasma was discussed in connection with burns While this is the most important cause of local plasma loss calling for the therapy outlined, it is not the only one Injury to a large part of the body may do it, but operations rarely are sufficiently extensive and traumatizing to cause local plasma accumulation or escape which calls for replacement therapy In the following case of common iliac vein thrombosis there was rapid loss of plasma into the limb which was sufficient to produce the circulatory failure A woman who was hospitalized with a generalized monilia of the skin, a suppurative otitis media, and an unrecognized carcinoma of the pancreas, developed, over night, a rapidly increasing swelling with mottling of the skin of the left lower limb When seen late in the forenoon she showed marked evidences of shock and no pulse was palpable in the markedly swollen and discolored extremity Her condition grew worse and she died at 7 P M , before which, however, the right limb also began to show slightly similar changes

At autopsy, there was found, aside from the above mentioned changes, a fresh thrombophlebitis completely blocking the left common iliac vein and partly blocking the inferior vena cava From measurements of the lower limbs, it was calculated that the volume of the left one was about four liters greater than that of the right There were no changes found to explain the immediate cause of death except the great loss of plasma into the limb

Most of the emphasis in the discussions was placed on the water, plasma and electrolyte needs of the patient and less on the accompanying erythrocyte needs which, obviously, may be difficult to separate

It should be borne in mind that in cases of marked postoperative circulatory failure, blood transfusion may be more efficient than fluid and electrolyte administration even though there has been no appreciable loss of blood at operation Also, this statement may sound like heresy but in sick patients who are to have extensive operations, it may, under circumstances, be advisable to operate more rapidly than usual, with greater blood loss and greater trauma to tissues in order to save the patient from prolonged general anesthesia The blood loss should be compensated for by blood transfusion (given simultaneously) One should balance all of the factors that come into play in an operation and utilize the ones that are least harmful, and time saved at the expense of some blood loss, if it is adequately treated by blood transfusion, may be of greater importance than meticulous hemostasis and a more prolonged operation

DR DAMON B PHEMISTER (Philadelphia, Pa) In considering what to say in the discussion of this symposium, with its breadth, width, and depth, I feel very much like Doctor Walter did this morning It is quite impossible even to touch upon all the various points of interest, and it seems to me better, therefore, to try to add one little point which has occurred to us in the Abington

Memorial Hospital as a result of our attempt to apply these plans and principles

Pardon me just a moment of reminiscence. At the next to the last Philadelphia meeting, which I think was 13 years ago, I read a paper on "Alkalosis Simulating a Case of Nephritic Uremia." That was just after Van Slyke had done his fundamental work on the p_{H} of the body fluids, pointing out the normal zones with the compensated zones on each side and the uncompensated zones and dangers. Acidosis was very much in the public eye, and the term "alkalosis" was just coming into use. Haden and Orr, Gamble and others had written very illuminatingly on the subject and explained certain deaths after upper abdominal operations as a result of dislocation of plasma structure. The pediatricians were quite alive to these humoral conditions as a result of the susceptibility of children to such abnormalities but the subject was, by and large, not at all diffused, certainly not to me, for I happened to have heard just enough of it to enable me to solve this one case.

The patient was a man who had had a long history of duodenal ulcer followed by a cicatricial stenosis and had formed the habit of vomiting. He could vomit almost at will and so pump out his stomach. He was brought into the hospital several times in a stuporous condition. His urine contained albumin, blood, and casts, and he was regarded and treated as a uremic. He was in deep coma and markedly dehydrated when I was asked to see him, not because I was expected to add anything as a surgeon but because I knew the family. In going over him, it struck me that it might be the new disease "alkalosis." His blood chemistry figures were as follows: Chlorides 200, plasma CO_2 80, and blood urea nitrogen 112. I suggested that instead of withholding salt on account of the supposed nephritis he be given sodium chloride in large quantities until his plasma chloride level was up to normal. This was done. As his plasma chlorides rose, the blood urea gradually fell, and about 24 hours later he began to come out, and the next day he was only a little confused, and the following day he was completely himself mentally. In a week I was able to perform a jejunostomy and later on a gastro-enterostomy. He got entirely well.

The importance of this case, and the fact that we were dealing with a hitherto unrecognized condition, impressed profoundly not only me but also Dr. John Eiman, who is now at Abington Memorial Hospital. For several years, the question of water balance and acid-base equilibrium has been the major surgical problem of the Abington Memorial Hospital to the extent that at times I fear we have made ourselves a little ridiculous. However, the problem as it has resolved itself to us is not so much any more in the understanding of the situation (although I am free to admit that we do not understand it at all, there is a great deal yet to be done) as in the difficulties we have in the correct application of these fundamental principles at the bedside.

We have developed rules which enable us to learn a great deal from the amount of urine. Dr. Walters, to-day mentioned that as long as the urine output was 1,000 cc or more, you could feel safe. That is true, by and large but there occur a few cases in which the situation is much more complicated and which require a great deal of acumen and, certainly, a modicum of chemical knowledge to determine just what is going on and what your replacement must be and how much. Furthermore, there are certain difficulties in getting the data that are necessary, that is the nurse, or the person who collects the specimens, must be absolutely accurate and must appreciate their importance. There must be somebody to supervise the nurse, to see that specimens are not thrown away. Then there is the question of recording. If you put them on the ordinary hour chart, it is a bit hard to dig them out and visualize what is

ABINGTON MEMORIAL HOSPITAL, Abington, Pa.

WATER AND SOLUTE CONTROL CHART

Another matter was the education of the younger men, the resident surgeon and intern. While we were so keen on the matter and discussing it all the time and talking about it in our stag meetings, everybody was keenly alive, "salt and water conscious," but when we could no longer afford to dwell so

much upon this matter, the successive generations came along without adequate instruction in the fundamentals. We found that we could not turn these things over to our younger men, as we do so many details, and very properly,

REVERSE OF WATER AND SOLUTE CONTROL CHART

THE purpose of this chart is to enable the clinician to evaluate grossly at a glance the state of hydration and solute balance in a patient. The amount of water held in the body is chiefly determined by the quantities of certain solutes contained in the body fluids, mainly the chlorides, bicarbonate, urea, and glucose. In normal concentrations urea and glucose play only a minor role but become important factors when the amounts are markedly increased.

For practical purposes the effective concentration of solutes in the blood can be estimated by adding the plasma chlorides, bicarbonate, and blood urea in terms of milliosmols. These fractions represent about 90% of all the crystalloids of plasma.

For more accurate studies all electrolytes measured by the total base, the total NPN, and glucose must be considered. This applies especially to cases in which the organic acids are markedly increased, as in starvation ketosis and in diabetes.

In the majority of normal cases the effective concentration of solutes in plasma, i.e., the sum of chlorides, bicarbonate, and urea, varies from 215 to 240 milliosmols. Cases showing values of 20 or more mOsm below or above the normal zone must be regarded as requiring prompt and special attention. This applies particularly to patients with large amounts of organic acids and high blood sugar.

Normal distribution of fluids between the capillaries and interstitial tissue spaces depends on the normal amounts and integrity of plasma proteins (Total 6-7.4 gms/100 cc, A/G ratio 1.5-1.8, colloid osmotic pressure 345-385 mm water). If patients are maintained on parenteral feedings for a week or more, special attention must be paid to the plasma proteins and deviations from the normal corrected by either whole blood or plasma transfusions. Unless protein faults are corrected, very little will be accomplished by the adjustment of the crystalloid imbalance.

If a patient depends mainly on parenteral intake, physiological saline should be substituted by Ringer's Solution after the third day. Further, in order to supply the vitamin requirements, such a patient should be given intravenously at least 50 mgms of Ascorbic Acid (in severe infections this should be increased to 60-100 mgms) and 1 mg Thiamin Chloride daily.

The upper part of this chart shows the concentration of plasma chlorides and bicarbonate in milliequivalents and the whole blood urea in millimols per liter. (Record the graphs as follows: Chlorides—green, Bicarbonate—blue, Urea—black.)

NORMAL ZONES	Plasma NaCl	560-600 mgms	% or 96-102 mEq/L
	Plasma CO ₂	45-65 vols	% or 19-26 mEq/L (bicarbonate)
	Blood Urea N	7-15 mgms	% or 3-6 mEq/L

CONVERSION VALUES

1. $\frac{\text{Plasma NaCl in mgms } \%}{5.85} = \text{chloride in mEq/L}$
Chloride in mEq/L $\times 1.86 = \text{mOsm}$
2. $\frac{\text{Plasma CO}_2 \text{ vols } \%}{0.43} = \text{bicarbonate in mEq/L}$
Bicarbonate in mEq/L $\times 1.86 = \text{mOsm}$
3. $\frac{\text{Blood Urea N mgms } \%}{2.8} = \text{Urea in millimols} = \text{mOsm}$
4. $\frac{\text{Phosphorus mgms } \%}{0.6} = \text{mEq/L}$
mEq/L $\times 1.86 = \text{mOsm}$
5. $\frac{\text{Glucose mgms } \%}{18} = \text{glucose in millimols} = \text{mOsm}$
6. $\text{Organic Acids in mEq/L} \times 1.86 = \text{mOsm}$
7. $\frac{\text{Proteins in gms } \%}{2.4} = \text{mEq/L} \times 1.86 = \text{mOsm}$
" " " " $\times 53.5 = \text{colloid osmotic pressure in mm water (when there is no A/G inversion)}$
Plasma Albumen in gms $\% \times 74.4 = \text{colloid osmotic pressure in mm water}$
Plasma Globulins in gms $\% \times 18.9 = \text{colloid osmotic pressure in mm water}$

NaCl is almost completely ionized when in a solution, thus $\text{NaCl} \rightleftharpoons \text{Na}^+ + \text{Cl}^-$; hence one part or one mol of NaCl yields almost 2 parts of ionic or osmotically active material. The ionization factor is 1.86 for all the electrolytes; therefore mEq/L of an electrolyte multiplied by 1.86 yields the number of milliosmols, mOsm. For non-electrolytes like urea and glucose, which do not ionize, the concentration in millimols, mM, and mOsm have been considered identical.

The middle part of this chart is a summation of the concentrations of Plasma NaCl, NaHCO₃, and urea expressed in milliosmols. This graph is recorded in red.

Normal Zone = 215-240 milliosmols

Attempt should be made to keep the red line within the normal zone by regulating the water, sodium chloride, and alkali intake.

On the lower part of the chart is recorded intake and output in 24 or if desired in 12 hours. Intake by mouth is recorded in black; parenterally in blue. Output—urine in red, drainage, Wangenstein, etc., in green.

Fluid intake should be adjusted to cover adequate urine output, drainage, and the insensible water loss. Normally the latter averages 800-1500 cc, but with fever and visible sweating the loss may be 2000-5000 cc a day.

An output of 500 cc of urine a day is to be regarded as an absolute minimum under those conditions the specific gravity should be 1.030 or better. In the event of diminished concentration with specific gravity around 1.020, the urine output should be maintained at 1000 cc or better.

I think. So it became a very great burden to the permanent staff to see that these matters of salt and water balance were properly adjusted.

We have felt for some time that we needed a more simple method of recording the pertinent data, something like a temperature chart, something that you could look at and see at a glance whether anything was going wrong,

without considering separately each item or figure. Then, with the cases that were out of balance you could take the time and trouble to investigate, draw your conclusions and institute the proper treatment. At last, we thought of a graph, you see, something like a temperature chart. You cannot just take the figures of salt and urea and CO_2 and add them up and build a chart. Urea, for instance, does not ionize, its value as an osmotic agent, therefore, is only about one-half of what salt and bicarbonate is. We needed a common basis for addition, so our biochemist, Doctor Grosscup, suggested expressing these components in milliosmoles, that is, in terms of equivalent osmotic pressure. Hence, we record the sum of the above substances as a red graph, the normal zone of which is between 215 and 240. It is desirable, but not essential, that we understand, in detail, the significance of the figures. As long as we provide for adequate urine output and keep the graphs within or near their normal zones, we have reasonable assurance that the patient's solute and water balance is close to normal. Watch the red line, especially if it is above or below its normal zone—bring it back promptly!

Now, taking a little note from Van Slyke, we say that anything 20 points above or 20 points below indicates a compensated zone but it also indicates danger. Above or below is a signal indicating that the patient is in imbalance and that something must be done at once to restore him. Hence, this is something like a temperature chart. You look at it, your graphs ought to be in their proper zones, and if they are not in there, why not? On the same chart we record in columns in different colors, oral and parenteral intake, also urine output and fluid losses through other channels. This helps to visualize at a glance what is going on. Further, we record the daily intake of glucose and sodium chloride intake and loss. Plasma proteins are estimated whenever indicated since we fully recognize their importance.

In order to have assurance of reasonably accurate collection of specimens and recording data and graphs, we had to put a special metabolic nurse on the job. We detailed her to go around to every tube-case and every case receiving fluids parenterally and see that the nurses were doing their work well. I do not think you are going to get sufficiently accurate data from a changing series of interns. I do not think your chief is going to be able to total these things up himself or herself, and the whole thing will fail unless you build up a mechanism to handle it accurately and without too much trouble.*

DR J. SHELTON HORSLEY (Richmond, Va.) The procedure of introducing the Abbott-Miller tube is often very valuable. Of course, it must be applied only in cases of obstruction in which there does not seem to be strangulation of the intestine or a serious affection of its blood supply, as in mesenteric thrombosis. In the type of obstruction following lymphatic adhesions or in adynamic obstruction it is valuable, though in some instances the tube is difficult to introduce.

The presence of an indwelling tube through the nostril, however, is not entirely innocuous, aside from the discomfort that it frequently gives, though in appropriate cases of obstruction these objections must often be endured for the relief that is obtained. Thus, Iglauer and Molt (Iglauer, Samuel, and Molt, Wm F. Severe Injury to the Larynx Resulting from the Indwelling Duodenal Tube. *Ann Otol, Rhinol and Laryngol*, 48, 886, December, 1939) report severe injury to the larynx from an indwelling duodenal tube occurring in ten cases which they have encountered. The tube was in place for periods varying from six to 20 days. Two patients died, and necropsy showed in one of them deep ulceration in the upper end of the esophagus, and in the

* These charts may be obtained by application to the author, at the Abington Memorial Hospital, Abington, Pa.

other, shallow linear ulcers in the upper end of the esophagus in the cicoid region. Both cases showed marked inflammation in the larynx. In the other patients, a tracheotomy was frequently imperative in order to relieve the acute laryngeal stenosis. They say that tubes of the smallest diameter should be used. Naturally the Abbott-Miller tube cannot be made as small as the Jutte or the Levine tube, so that trauma may be even greater.

Doctor Abbott has shown, in his illustration, that his tube is used after a gastro-enterostomy, being inserted through the nose, into the stomach and into the jejunum so that nourishment can be given.

I wish to call attention to a simple procedure that I have been using for the last few years after pyloroplasty, partial gastrectomy or gastro-enterostomy, which avoids the necessity of having an indwelling tube through the nose. In a gastro-enterostomy, for instance, after the posterior layer of sutures has been placed a sharp-pointed hemostat is introduced through the opening in the stomach and thrust through the anterior wall of the stomach. It catches a medium size soft rubber catheter in which there are two openings. The catheter is clamped about its middle, and is drawn into the stomach for about three inches. It is fastened to the stomach with fine chromic catgut, and around this is placed a purse-string suture of the same material. The gastro-enterostomy is completed, and then a stab wound is made to the left of the abdominal incision and the butt of the catheter is drawn through the stab wound. The stomach is fastened to the parietal peritoneum with fine chromic catgut, and a tag of omentum is also brought around this region.

If it is desired to give nourishment, a longer tube, such as the Jutte tube, can be used instead of the catheter, and can be brought down well into the jejunum.

Thrusting a sharp-pointed hemostat through the stomach wall instead of cutting the stomach does not destroy the muscular layers of the viscus, and when the tube is removed there is usually no leakage of stomach contents. The tube can be kept in indefinitely, and affords not only a means of emptying the stomach contents and relieving the strain on the sutures, but, if placed in the jejunum, may be an avenue of supplying nourishment via the jejunum.

DR WALTER ESTELL LEE (Philadelphia, Pa.) Doctor Minot has referred to the reactions which follow the use of blood serum, and I would like to call attention to the fact that these reactions are even more severe and more frequent when lyophilized serum is administered intravenously. Doctors Stokes and McGinnis, in the Children's Hospital in Philadelphia, developed, some years ago, a practical method for the preparation of lyophilized blood serum, and they established at the hospital a Bank (which they called a Station) and undertook to supply dried lyophilized serum from the blood of immunes who had had various contagious diseases, such as measles, infantile paralysis, influenza, scarlet fever, *etc*. However, the hopes for this plan have not materialized because it has been found that the reactions were so frequent and severe that the whole scheme has been practically abandoned. Minot has called attention to the fact that these reactions do not occur when plasma is employed instead of sera and further, that agglutination does not occur with plasma as in serum, which eliminates the necessity for typing and matching of the donor and the recipient. This has been found true not only when the plasma is fresh, but also when it is pooled as a by-product from a Blood Bank. In Philadelphia we have discontinued the use of whole blood from a Blood Bank after it has reached the age of four days, and the plasma obtained from these Banks has provided a source of supply which, in most hospitals, has been entirely adequate to meet the increasing demands for

plasma These demands are increasing rapidly, and, at the present time, in many of the hospitals whole blood is never administered unless there is a specific need for red blood cells Recently, Doctor Strumia, at the Bryn Mawr Hospital, which is in one of the suburbs of Philadelphia, in reporting his experiences with plasma instead of serum and whole blood, over a period of three or four years, also records his work with lyophilized plasma, the results of which are comparable in every way with those he has obtained with fresh plasma To us, this seems to be a remarkable contribution, particularly in the present military crisis The possibility of preparing lyophilized plasma and storing it in glass ampules and shipping it where it may be most needed, would obviate the need for preservation by refrigeration of blood, classification by types, and the cross-matching before a transfusion is administered The mere mixing of the lyophilized plasma with sterile saline solution will provide a plasma for transfusion which probably will meet the requirements in most of the acute emergencies in military surgery

DR A S MINOT (Nashville, Tenn, closing) I have listened with interest to the discussions about estimating the need for fluid and electrolyte I should like to add a suggestion in regard to the estimation of whether or not replacement therapy is keeping up with the loss of plasma volume When we start to treat a patient we do not know how extensive the capillary damage may be If it is mainly a question of overcoming dehydration and supplying the necessary fluid and electrolyte, then the intravenous administration of fluid is most valuable in restoring and maintaining the circulation Under these circumstances the concentration of plasma protein and of cellular elements of hemoglobin should dilute together as fluid is restored On the other hand, if one makes, as so often happens, the paradoxical observation that the cells are becoming more concentrated in the blood while the plasma protein concentration is progressively decreasing, it can only mean that plasma fluid and protein are being lost from the blood stream Thus, by making frequent measurements of the hemoglobin concentration and by determining the plasma proteins either chemically or by specific gravity, we have a means of knowing whether the administration of fluid is restoring and increasing the plasma volume or is having the opposite effect With this information as a guide the replacement therapy can be adapted more closely to the needs of the particular patient

DR W OSLER ABBOTT (Philadelphia, Pa, closing) The question of nasal irritation from the presence of tubes is one which, I think, deserves a word That is often the factor determining the time for which the tubes can be left in place Throughout this period, extreme care must be given the nose and throat to keep the mucosa shrunk away from the tube, so that drainage of nasal secretions will be free Irritation should be relieved, insofar as possible, by the use of local applications The actual erosion of the nasal pharyngeal surfaces, however, as far as I can determine, occurs more commonly at the time of the withdrawal of the tube than while it is in place, though I say this with the realization that it must in some cases be unavoidable in the course of time I should like to place the emphasis on careful withdrawal so that the erosions are not produced by actual mechanical friction of the tube through the nasopharynx

DR ROBERT ELMAN (St Louis, Mo, closing) I should like to discuss for a moment Doctor Fine's paper, which I feel is a very important contribution to the treatment of intestinal obstruction I should like to present one case in confirmation of his findings, with a reversal, however, in the thera-

peutic approach Doctor Fine remedied the loss of plasma in his patients by correction of the distention, in my case I remedied the distention by correcting the loss of plasma

Chart 1 represents observations upon a child who was operated upon for rupture of the appendix, with general peritonitis The recovery following operation was uneventful until the seventh day when she developed abdominal distention and vomited, and, in spite of decompression, remained distended—severely so, more alarming than that, was the general condition of the

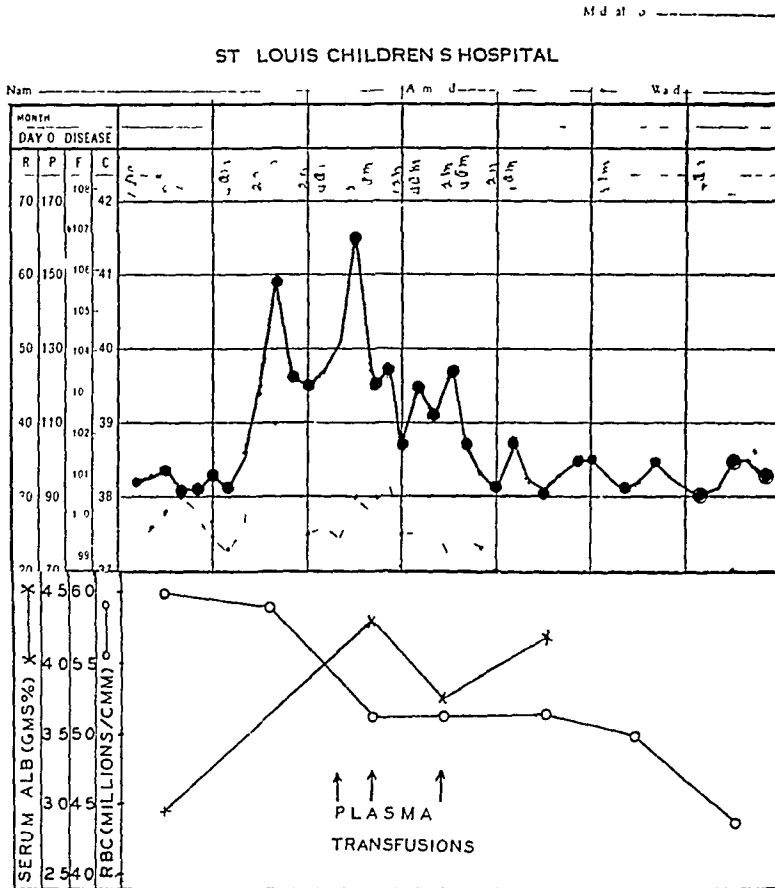


CHART 1—This represents the findings from the seventh to the fourteenth day following operation for a ruptured appendix, with generalized peritonitis, in a female child weighing 20 Kg. The course was uneventful up to the seventh day, when distention and vomiting began, circulatory collapse developed the next day. Prompt relief following the plasma transfusions (each of 200 cc) coincided with the return of the various measurements to normal as shown in the chart. In the upper curves the heavy line represents the pulse rate the light one the temperature, in the lower curves the red blood count and serum albumin concentrations are indicated in the left margin.

patient which, as indicated by the chart, had produced an extraordinary increase in the pulse rate. She was semicomatose. Her color was poor. The red cell count was 6,000,000, serum albumin, which we feel is more important than the total serum protein, had fallen below 3 Gm per cent. In spite of the fact that she was receiving the usual amount of parenteral fluid, she excreted but little urine. At the points indicated by the arrow, three plasma transfusions were administered because we felt her dehydration was due to the loss of a great deal of plasma somewhere.

I should like to call your attention to the large dose of plasma that was

given this particular patient. Each injection consisted of 200 cc, which represented 10 cc per Kg of body weight, since the child weighed 20 Kg. This same dose was repeated three times within the next 36 hours. This would correspond, in an adult, to the administration of 2,100 cc of plasma.

The striking thing was the remarkable clinical effect of the plasma transfusions. As can be seen in the chart, there was a fall in the pulse rate, her general condition improved. She became alert. Her color improved. The red count fell promptly, and then became normal. The serum albumin rose to normal (4.3 Gm per cent). She began to pass flatus and stool, and we were very gratified when the distention disappeared. She recovered completely, without the necessity of any further operative procedure.

This patient, obviously, suffered an extreme degree of plasma loss, the nature of which we were unable to determine, except that, I agree with Doctor Fine, it must have been lost somewhere in the gastro-intestinal tract. Regardless of the cause, however, the result of plasma transfusion in large amounts was a true example of replacement therapy and coincided, in many respects, with the results we have observed with similar treatment in severe cutaneous burns, which was so perfectly, and amply demonstrated by the case which Doctor Minot reported.

DR CARL W. WALTER (Boston, Mass., closing). I should like to emphasize that solutions which have been prepared properly and sterilized for 30 minutes at 250° F will keep indefinitely provided they are hermetically sealed. The present, almost universal custom of discarding such solutions after periods of 48 hours to five days is uneconomic, and there is no basis in fact for discarding them.

The second point is that careless sterilization may spoil solutions as far as the clinician is concerned. If the sterilizer operator vents the steam pressure in the sterilizing chamber, solutions at 250° F are suddenly subjected to atmospheric pressure. Such solutions are then superheated. To relieve this superheat, steam is evolved, and this sudden ebullition of steam causes concentration of the solution. Frequently, the steam in the chamber is vented, while that in the jacket is left on. The solutions are thus gradually boiled away. Accordingly, instead of using isotonic solutions, the clinician may often be using hypertonic solutions. This can be avoided by being certain that the steam supply to the sterilizer is turned off at the end of the sterilizing cycle, and that the autoclave door is securely closed until the temperature of the solution has reached 212° F, where superheat no longer exists and concentration due to evaporation will not occur.

GASTRIC ACIDITY BEFORE AND AFTER OPERATIVE PROCEDURE WITH SPECIAL REFERENCE TO THE RÔLE OF THE PYLORUS AND ANTRUM^{*}

A PRELIMINARY REPORT OF A CLINICAL AND EXPERIMENTAL STUDY

OWEN H. WANGENSTEEN, M D ,

RICHARD L. VARCO, M D ,

LYLE HAY, M D ,

STEWART WALPOLE, M D ,

AND

BENEDICT TRACH, M D

MINNEAPOLIS, MINN

FROM THE DEPARTMENT OF SURGERY UNIVERSITY OF MINNESOTA MEDICAL SCHOOL MINNEAPOLIS, MINN

THIS STUDY has as its objective definition of what operative procedure, upon the stomach, accomplishes in the management of duodenal and gastric ulcer. This effort represents an attempt to assay the effects of the commonly practiced operative procedures such as gastro-entrostomy, antial excision and extensive gastric resection upon gastric acidity, and to correlate these findings with the effect of these same operations upon gastric evacuation. The effects of tubular resection with and without gastrojejunostomy and the Schmilnsky operation, in which provision for complete intragastric regurgitation of duodenal content is effected, together with antial excision, upon gastric acidity and evacuation will be reported as well.

Despite studies made upon the physiology of gastric secretion, the factor or factors which determine whether the parietal cells of the acid secreting area of the stomach will or will not secrete free hydrochloric acid remain an enigma still. The importance of acid in the genesis of ulcer has been established definitely by the experiments of Mann and Williamson, and Dragstedt and his associates. Mann and Ivy and their associates, though stressing the importance of the acid factor in the genesis of ulcer, have pointed out repeatedly the importance of the mechanical factor. Moreover, the experiments of Matthews and Dragstedt may be construed to suggest that acid is *the* factor or common denominator of ulcer. The larger number of observers and experimenters are in agreement with Ochsner and his associates that acid is only an important factor in the genesis of ulcer. Other items, such as trauma, the nervous factor and deficiency states, are believed to play a significant rôle.

The operative procedures performed by surgeons for relief of uncomplicated chronic duodenal and gastric ulcer causing pain have largely an empiric

* Read before the American Surgical Association, St. Louis, Mo., May 1, 2, 3, 1940.

The researches presented here were supported by grants of the Graduate School of the University of Minnesota and the Committee on Scientific Research of the American Medical Association, and by a grant for technical assistance by the Works Projects Administration, Official Project No. 665-71-3-69, Sub-project No. 58.

basis Through what agency the beneficial effects of operation upon the stomach for ulcer are mediated is still a matter of some speculation and considerable difference of opinion It is not without interest that the favorable influence of gastro-enterostomy upon a duodenal ulcer has been ascribed successively through the years to (1) Physiologic rest for the ulcer, (2) improved drainage from the stomach (decreased gastric evacuation time), (3) increased intragastric regurgitation affording opportunity for greater dilution and neutralization of the acid gastric content, and (4) effective reduction of gastric acidity

Those who advise or practice gastric resection for ulcer set as their objective the attainment of achlorhydria in the residual gastric segment If the weight of evidence were to be evaluated from the literature in terms of expressions from persons interested and experienced in the field, one would be forced to conclude that the "small gastric resection" (partial), whether performed by the Billroth I or II plan, is an eminently satisfactory operation, insuring achlorhydria—not always but usually achieving this effect through sacrifice of the pylorus and antrum, sometimes described as the acid regulator, awakener or titillator of the acid secreting glands in the corpus and fundus A large number of surgeons favor the "small gastric resection" (partial) for ulcer Among others are Friedmann, Fromme, Goetze, Haberer, Hoffman, Konnecke, Lorenz and Schui, Rieder, Rienhoff, and Smidt

There are, of course, dissenting opinions to this expression On the one hand, there are those who insist that, whereas antral excision will not insure achlorhydria, a more aggressive excision of the acid secreting area of the stomach will (Finsteier) On the other hand, there are those who suggest that excision of increasingly larger segments of the stomach ("subtotal resection") is not more likely to succeed in making the stomach achlorhydric than is the small gastric resection (partial), and that an extensive gastric resection is just as likely to be followed by an anastomotic ulcer (Shapiro and Berg, and Lewis) The dissenters in this latter group from extensive gastric resection disapprove of the operation for two different reasons The one, because they feel that the stomach cannot be made achlorhydric as long as any gastric tissue remains, the other, because they feel that gastric resection *per se* is the wrong approach to the whole problem, believing that acid, after all, plays only a small, if any, part in the origins of ulcer (Emery) Others approve of extensive gastric resection for ulcer, but do not believe that gastric acidity *per se* has much to do with the etiology of ulcer (Konjetzny, Mizoguti, and Tomoda and Aramaki) An increasing number of surgeons have found that extensive gastric resection, though not affording the patient absolute protection against recurrent ulcer, is more likely to exhibit fewer failures (A A Berg, Finsteier, Graham, Klein, Lahey, Lewisohn, Ogilvie and Strauss)

Were one of us to set ourselves the laudable task of reading all that has been written upon the mechanism of gastric secretion the genesis of ulcer and its treatment, a long life of ardent study would not suffice to encompass

the entirety of these intimately related subjects. Moreover, it is even more significant that crucial experiments to secure direct and final answers to these issues have not yet been devised. Ivy, an experienced and successful experimentalist in the field of gastric physiology, said (1931) in a moment of discouragement, "I have been working on the question of ulcer for about 12 years, and I am about to give it up, for the simple reason that I know of no way of producing a pylorospasm or reflex nervous disturbance in a dog, as they are known to occur in man, due to emotions and anxiety with their associated motor and secretory disturbances."

It is obvious that the stomach is a very complex and intricate organ, the functions and mechanisms of which are not wholly understood.

The Edkins' Hypothesis—One of the chief objectives of this study has been to investigate the validity of the Edkins' hypothesis. Pavlov, it is to be remembered, divided gastric secretion into three phases: (1) The psychic or cephalic phase, in which sight, smell or taste of food set up impulses which reach the stomach by way of the vagi nerves, causing a flow of gastric juice. On sham-fed esophagotomized dogs, Pavlov was able to show that vagotomy inhibited psychic secretion of gastric juice. (2) The gastric phase, contingent upon the presence of food in the stomach—elicited by a large variety of foods including water. Whether hydrochloric acid, secreted in response to the presence of food in the stomach, is excited through a secretagogue or hormonal effect is not known. (3) The intestinal phase occasioned by the digestion of food in the intestine and its absorption.

When surgeons adapted gastric resection, which Billroth executed successfully for the removal of gastric cancer, to the surgery of ulcer, it is natural that the same pattern of excision of gastric tissue should have been employed for the management of gastric ulcer. With elaboration of Edkins' hypothesis that gastrin, a pyloric and antral hormone, regulated and controlled the gastric phase of gastric secretion, sufficient justification seemed to have been found for the surgeon's practice of excision of the pylorus and antrum to reduce gastric acidity—a practice which came to be applied later, with even more vigor in certain quarters to the treatment of duodenal ulcer.

The validity of the Edkins' hypothesis of pyloric hormonal control of the gastric phase of gastric secretion is still a matter of no general agreement. Ivy (1930) reviewed the experimental data for and against pyloric hormonal control of the gastric phase of gastric secretion, and concluded that the question could not be answered definitely and finally until it could be determined whether or not purified preparations of gastrin from the antral mucosa were chemically identical with histamine. On the experimental side, too, there is considerable disagreement as to the effect of removal of the pylorus and antrum upon gastric secretion. Among those who insist that results of the sacrifice of the pylorus and antrum in the dog (antral excision plus gastrojejunostomy) uphold the Edkins' hypothesis are Smidt (1923), who observed a shortening of the gastric phase of gastric secretion and a lowering of acidity, and Wilhelmj, and O'Brien and Hill (1936), who observed definite lowering

of gastric acidity Priestley and Mann (1932), while reporting somewhat inconstant results, concluded that the pyloric mucosa played only a minor rôle in the regulation of gastric acidity Lewis (1938) excised the antral mucosa, leaving the musculature of this gastric segment intact He observed marked reduction in gastric acidity, but the response to the histamine test remained normal Enderlen and Zukschwerdt (1931) demonstrated lowering of gastric acidity in Pavlov pouches in dogs after antral excision, but observed that, in time, the acidity returned to normal London (1925) has noted this same occurrence

Portis and Portis (1926), employing a Pavlov pouch, were unable to detect any significant difference in the secretion of the pouch after antral excision The residual stomach anastomosed to the jejunum they found to be consistently achlorhydric Shapiro and Berg (1934) confirmed these findings, failing, however, to observe achlorhydria consistently in the residual portion of the stomach anastomosed to the jejunum The observations of Steinberg, Brougher and Vidgoff (1927) are in general agreement with those of Portis and Portis, and Shapiro and Berg—all of which tend to discredit the Edkins' hypothesis, as well as the practice of antral excision, as an effective means of reducing gastric acidity in the management of ulcer

On the clinical side, however, as indicated above, expressions from those who have applied the Edkins' hypothesis to ulcer management suggest quite strongly that antral excision is an effectual and satisfactory means of reducing gastric acidity

The Authors' Approach to the Problem—In essaying to evaluate the accomplishments of operation in the management of ulcer, as well as the manner in which the effects of operation are mediated, we have regarded surgical therapy as an experimental approach to the ulcer problem A most conservative attitude regarding the rôle of surgery in the management of ulcer has been entertained by both internists and surgeons in the clinics of the University Hospital Up until recently, gastro-enterostomy was the commonly practiced operative procedure in those patients presenting classic and somewhat pressing indications for operations, save for the gastric ulcer which was suspected of being malignant Gastric resection has been performed regularly for gastric ulcer when the roentgenographic defect persisted despite rigidly controlled dietary management and bed rest With some mutual misgivings, entertained by both internists and surgeons over the accomplishments of gastro-enterostomy and with the consent of the Department of Medicine, the surgical staff, while still adhering strictly to orthodox indications for operation, chose to vary the type of surgical procedure, with the consideration in mind of garnering useful information concerning the rôle of various operations in the management of ulcer, as well as the manner in which such influence is mediated

In addition, in the laboratory a variety of experimental procedures have been carried out, largely upon the dog, in an attempt to assay further the validity of the Edkins' hypothesis These experiments will be cited briefly

here, together with some work still in the process of prosecution which lends increased credence to the significance of acid as a most important factor in the genesis of ulcer, as suggested in the experiments of Mann and Williamson, and Matthews and Dragstedt

The Clinical Data—It was the occurrence of gastrojejunal ulcer in two patients, subjected to antral resection because of continued bleeding from a duodenal ulcer, that suggested this study. Both patients (Cases 1 and 2, Table II) had had a previous gastro-enterostomy, and when the antral resection was performed, no evidence of a gastrojejunal ulcer was observed in either instance. In both patients, gastrojejunal ulcer followed antral excision within a few months.

Sixty patients having the following types of operative procedure were available for study

- Group I Twenty-nine cases gastrojejunostomy—retrocolic
- Group II Six cases antral excision, with complete terminolateral anastomosis (Pólya)
- Group III Ten cases extensive gastric resection including pylorus and antrum, with either partial (Hofmeister) or complete retrocolic terminolateral anastomosis (Pólya). Entero-anastomosis was performed in some, in others it was omitted.
- Group IV Six cases antral exclusion, with extensive gastric resection (Finsterer's operation) accompanied either by partial (Hofmeister) or complete retrocolic terminolateral anastomosis (Polya). Entero-anastomosis was more often performed than omitted. This operation was undertaken in instances of duodenal ulcer with choledochoduodenal fistula and in other instances of duodenal ulcer in which there was a good deal of induration of the duodenum, extending in a few instances into the prepyloric region. The segment of stomach remaining proximal to the pylorus followed in all instances Finsterer's admonition of leaving not more than two fingers' breadth of gastric tissue.
- Group V Three cases—provision for complete intragastric regurgitation for gastrojejunal ulcer following antral excision (Schmilinsky operation). Cases 1 and 2 of this group appear also in Group II.
- Group VI Five cases tubular excision (fundus and corpus) with gastrojejunostomy, leaving the antrum and pylorus intact.
- Group VII Three cases tubular excision (fundus and corpus) without gastrojejunostomy, leaving the antrum and pylorus intact.

In those instances operated upon within the last year, careful note was made of the amount of gastric tissue excised at operation. In the earlier cases, extensive gastric resection was performed for high-lying gastric ulcer, in duodenal ulcer, gastro-enterostomy was the common operative procedure. Antral excisions were done for bleeding duodenal ulcer and the occasional gastric ulcer situated near the pylorus.

In all patients, carefully controlled postoperative studies of gastric acidity have been made. In most patients, including all the resections, such preoperative data are available. The postoperative observations made upon these patients include (1) Studies of gastric acidity, (2) gastric emptying time, employing the neutralization test (introduction of 150 cc of 0.4 per cent HCl into the stomach), and (3) gastric evacuation time, determined fluoroscopically, after the patient swallowed 150 cc of a thin barium mixture. The emptying time for barium was 83 minutes in a small group of normal persons (Bergh).

The gastric acidity was determined by the usual colorimetric titration, employing Topfer's reagent as the end-point for free hydrochloric acid and phenolphthalein as the end-point for the total acid.

Gastric acidity was determined regularly in the morning, the patient having had no breakfast. A No. 14F duodenal tube with four perforations at the tip was introduced through the nose into the stomach, and periodic aspirations were made as follows: (1) Fasting, (2) 30 minutes after intragastric instillation of alcohol (50 cc of 7 per cent solution), and (3) 30, 60 and 90 minutes after 0.5 mg of histamine hydrochloride.^{*} In the "neutralization test," acid was introduced into the fasting stomach and aspirations were made at subsequent intervals of 15, 30, 45, 60, 75 and 90 minutes. The figures in the table indicate the amount of acid "neutralized or lost" in one hour. In the graphic sketches of the results of this test, we have employed the normal standard described by Elman. This test is probably described more accurately as a test of the gastric evacuation time. Control studies with barium suggest a fairly close parallelism between the ability of the stomach to "neutralize" acid and rapid evacuation. That is, a stomach that emptied rapidly with barium also showed a great capacity to "neutralize" acid introduced. We have come to speak, therefore, of acid loss, through rapid gastric emptying rather than neutralization.

We have chosen to put a good deal of emphasis upon the results of the histamine (maximal) stimulation, feeling that these findings are most significant. It is to be admitted freely that histamine, in a sense, is not a physiologic activator of gastric secretion. That is, histamine does not give a maximal stimulus alike to the secretion of pepsin and mucus, as it does to hydrochloric acid. Yet, the subcutaneous injection of histamine evokes the maximal known stimulation of acid secretion from the gastric glands and constitutes, therefore, a real test of the ability of operative procedures to make the stomach achlorhydric. It might reasonably be asked whether one should not regularly expect evidence of active secretion of hydrochloric acid after histamine as long as any normal gastric tissue remained, no matter what type of operative procedure had been performed. Interestingly enough, however, as the data will indicate, the procedure and the amount of tissue removed have an important answer to give to this question.

^{*} One-half milligram of histamine hydrochloride represents 0.3 mg of histamine base.

The data are summarized briefly in tables corresponding in number to the groups listed above

TABLE I
PATIENTS HAVING GASTROJEJUNOSTOMY

Name Hosp No Age—Diag Oper — Date	Date of Analysis	Fasting Free Acid	Maxi- mum Free with Hista- mine	Maxi- mum Total with Hista- mine	Volume of Secre- tion $\frac{1}{2}$ hr (in Cc)	Acid Output Mg $\frac{1}{2}$ hr		Acid Neu- tralized % Acid Loss	Mo- tility Emp- tying Time —Ba
						Free	Total		
(1) Mrs L L * 685777 59—D U G J —9/6/20	10/24/39	0	0	32	12 0	0	14 0	93	
(2) Mr H H 690290 40—D U G J —1927	1/23/40	20	8	32	18 0	5 0	21 0	94	195 min
(3) Mr A S 656876 55—G U and D U G J —1927	3/18/40	0	84	102	9 0	27 6	32 2		60 min
(4) Mr E F 617977 54—D U G J —8/28/33	2/27/40	32	34	54	11 0	13 6	21 6	90	
(5) Mrs J R 606079 62—D U G J —3/23/34	2/6/40 4/17/40	14 40	80 57	96 67	3 5 4 7	10 3 9 0	12 3 10 0	94	30 min
(6) Mr R Z 674760 60—D U G J —4/1934	2/32/40	12	56	74	18 0	36 8	48 6	93	60 min 15 min
(7) Mr V C 624155 67—D U G J —7/25/34	1/22/34 1/27/34 11/10/39 2/8/40	51 12 + 60	50 0 0 37 5	66 28 77 5	9 0 4 6	0 6 3	18 4 13 5	100 98	
(8) Mrs A S 630909 38—P U † G J —10/12/34	9/8/34 11/12/39 2/29/40 4/4/40 4/27/40	0 0 0 0 0	0 0 0 0 0†	28 36 20 40†	13 4 2 7 2 0 1 2	0 0 0 0	13 5 3 6 1 46	88 79	40 min
(9) Mr H M 617859 31—J U G J —1/2/35	11/7/39	0	50	62	14 3	25 5	31 0		

TABLE I (Continued)

Name Hosp No Age—Diag Oper — Date	Date of Analysis	Fasting Free Acid	Maxi- mum Free with Hista- mire	Maxi- mum Total with Hista- mine	Volume of Secre- tion ½ hr (in Cc)	Acid Output Mg ½ hr		Acid Neu- tralized % Acid Loss	Mo- tility Emp- tying Time —Ba
(10) Mrs J F 641350 71—D U G J —10/15/35	2/21/40	13 5	50	60	22 0	40 0	48 0	86	115 min
(11) Mrs R S 620111 66—D U G J —10/18/35	3/6/40	0	62	72	7 0	15 6	18 4	87	80 min (95%) empty
(12) Mr F M 645426 69—G U G J —7/28/36	2/21/40 4/4/40 4/17/40	0 0 24	0 50 34*	22 62 44†	9 8 6 2 13 0‡	0 11 2 16 2	7 8 15 0 21 0	98	60 min
(13) Mrs C H 652147 55—G U G J 9/30/36	1/15/36 5/9/38 2/6/40	0 0 50	62 78 98	80 98 110	13 0 6 0 14 0	29 4 17 1 50 2	37 8 21 6 56 0	69	60 min
(14) Mr W P 655113 42—D U G J —1/11/37	3/25/40	62	116	132	17 0	72 0	82 0		95 min
(15) Mr J J 656061 32—D U G J —6/9/37	2/20/37 2/26/40	0 24	0 46	12 58					
(16) Mr F W 661275 40—D U G J —6/1937	2/29/40 4/9/40	0 50	0 72	100 80	0 5 30 0	0 78 4	1 8 87 4	98	95 min
(17) Mr W P 659892 50—D U G J —8/18/37	2/19/40 4/26/40	15 0	32 50	44 60	5 0 28 0	5 8 51 0	8 0 61 0		15 min
(18) Mr O W 661145 60—D U G J —9/9/37	2/19/40	60	82	98	26 0	78 0	93 2		
(19) Mr C W 659895 56—G U G J —9/9/37	6/24/37 12/8/39 2/8/40	20 0 64		36 68 56	3 1 4 0	3 8 5 8	7 5 8 1	97 93	12 min 15 min 14 min

TABLE I (Continued)

Name Hosp No Age—Diag Oper— Date	Date of Analysis	Fasting Free Acid	Maxi- mum Free with Hista- mine	Maxi- mum Total with His a mine	Volume of Secre- tion $\frac{1}{2}$ hr (in Cc)	Acid Output Mg $\frac{1}{2}$ hr		Acid Neu- tralized % Acid Loss	Moti- lity Emp tying Time —Ba
(20) Mr J K 666254 58—D U G J —3/3/38	2/16/38 11/8/39	0 12	20 74	30 92	9 0 14 0	6 5 37 6	9 2 30 0	89	-----
(21) Mr M B 636231 55—D U G J —11/25/38	2/8/40	48	50	68	14 0	25 5	34 6	92	3 hr 30 min (65% empty)
(22) Mr R M * 637026 39—D U G J —12/19/38	2/21/40	0	0	16	3 0	0	1 75	96	30 min
(23) Mr L J 672742 30—D U G J —12/28/38	2/7/40	68	84	94	16 0	49 0	54 0	86	40 min
(24) Mr A W 648654 54—D U Perf sutured 7/28/37 G J —1/31/39	5/12/36 1/29/38 4/25/39 11/8/39 3/5/40	37 21 0 38 18	 71 8 28 0	 80 18 44 18	 17 0 18 47 0 11 0	 44 0 0 47 0 0	 49 5 75 0 7 2	 100	 85 min
(25) Mr O N 668719 73—G U G J —7/13/39	5/8/38 6/22/39 10/24/39 12/28/39 3/29/40 4/16/40	24 0 0 0 0 0	 0 0 0 32†	 55 22 40†	 1 9 4 1 7 2	 0 0 8 3	 3 0 3 2 10 4	 94 97	 30 min 80 min
(26) Mr R E 672523 29—D U G J —10/25/39	2/19/40 4/15/40	0 22	10 76*	18 92*	12 0 10 0	4 4 27 0	7 9 33 0	96	1 hr
(27) Mr W W * 686536 51—G U G J —11/6/39	10/31/39 11/20/39 11/22/39 11/25/39	28 0 0 0	86 0 0 0	100 25 40	67 0 10 6 67 0	210 0 0 0	248 0 9 2 97 0	42 97	--
(28) Mr H E 688048 38—D U G J —12/21/39	12/21/39 1/20/40 1/22/40	64 0 12	96 25 38	110 55 78	15 0 4 6 7 0	52 0 4 7 9 6	61 0 10 2 20 0	90 83 96	--

TABLE I (Continued)

Name	Amount			Maxi- mum	Maxi- mum	Volume	Acid Output		Acid	Mo- tility
Hosp No	Resected		Fasting	Free	Total	of	(Histamine)		Neu- tralized	Emp- tying
Age—Diag	(in sq	Date of	Free	Hista- mine	Hista- mine	Secre- tion	Mg ½ hr		% Acid	Time
Oper Date	cm)	Analysis	Acid			(in Cc)	Free	Total	Loss	—Ba
(29)										
Mrs D V	12/31/39	20	65	73	18 0		42 0	48 0	77	
686531	1/2/40	0								
50—D U	2/5/40	0	38	62	20 0		27 4	45 0	86	
G J —12/22/39	4/26/40	16	22†	32†	18 0		14 4	21 0		

* Not available for verification with triple histamine

† Possibly luetic gastritis

‡ Specimens taken 30 minutes after three successive injections of 0.5 mg of histamine

Abbreviations G U = gastric ulcer

D U = duodenal ulcer

P U = pyloric ulcer

G J = gastrojejunostomy

RESULTS

GROUP I—GASTROJEJUNOSTOMY

It is to be noted that the reduction in gastric acidity after gastrojejunostomy is slight. There are a few patients who have been achlorhydric, at least on one occasion. However, *not a single patient* with a well-authenticated record of ulcer has been achlorhydric after the administration of 1.5 mg of histamine in triple doses of 0.5 mg given one-half hour apart. These findings confirm the statement of Holman and Sandusky, who found that achlorhydria was a rare occurrence after gastrojejunostomy for ulcer.

That a number of patients having gastrojejunostomy became free of symptoms is well known and suggests that the operation has some virtue. The rapid loss of hydrochloric acid from the stomach in the neutralization test and the decreased emptying time with barium suggest that the value of gastrojejunostomy lies in the more rapid emptying of the stomach (Fig 1).

GROUP II—EXCISION OF ANTRUM AND PYLORUS

There are six patients in this group. Without exception, all these patients had their operation for massive hemorrhage from duodenal ulcer. In four instances, a preliminary gastrojejunostomy was performed. In all instances, save the first, the interval between gastrojejunostomy and excision of pylorus and antrum was only a few days to a few weeks or months. In the first patient in the group, the interval between gastrojejunostomy and excision of the pylorus and antrum was more than 12 years. In this patient, unfortunately, no studies of gastric acidity were made until several months after the Schmilnsky operation had been performed for gastrojejunal ulcer occurring after antial excision.

This patient has exhibited achlorhydria occasionally after histamine. As recently as September, 1939, almost four years after the Schmilnsky operation, he was still not achlorhydric on histamine stimulation. After the administration of triple doses of 0.5 mg of histamine given at intervals of half an hour, gastric analysis showed free hydrochloric acid to be present. One other

TABLE II

PATIENTS HAVING EXCISION OF ANTRUM AND PYLORUS*

*Small Gastric Resection**All Complete Terminolateral Anastomoses—No Entero-anastomoses*

Name	Amount Resected (in sq cm)	Date of Analysis	Fasting Free Acid	Maximum Free with Histamine	Maximum Total with Histamine	Volume of Secretion ½ hr (in Cc)	Acid Output (Histamine) Mg ½ hr		Acid Neutralized % Acid Loss	Motility Emp tying Time —Ba
(1)										
Mr F F †		5/29/34	7	8	16					
627911		4/19/35	16	70	82	67 0	175 0	198 0		
49—D U		12/31/36	0	0	23					
G J —1918		9/5/39	0	9	39	12 0	5 9	26 0		
Ant Resect		3/11/40	0	0	30	16 0	0	13 0		160 min
4/20/35										
Schmilinsky										
1/8/36										
(2)										
Mr C M		1/20/34	0	53	63					
623906		11/11/36	0	0	32	20 0	0	23 2		
49—D U		11/14/36	13	0	20	1 5	0	2 11	100	
G J —11/14/38		2/26/40	0	34	52	13 0	15 0	25 0	95	30 min
Ant Resect		4/4/40	30	68	72	31	7 7	8 1		
12/17/38	138									
(3)										
Mr L K ‡		5/25/38	30							
669044		6/13/38		80	100					
24—D U		4/18/39	52							
G J —2/14/39		5/8/39	0	38	50	9 0	12 3	16 4		
Ant Resect		5/15/39	31							
2/21/39										
Schmilinsky		6/28/39	24							
with excision of a portion of fundus		8/29/39	0	26	40	15 0	14 3	22 0		
5/15/39	110									
(4)										
Mr L W		8/29/39	24	**	71					
643715		11/8/39	0	0	60	2 0	0	4 3	58	
50—D U		2/21/40	0	18	36	11 0	7 24	14 3	79	155 min
9/3/39	130	4/10/40	0	0	24	12 0				
		4/22/40	0	18§	65§	1 7	1 1	4 0		
(5)										
Mr C B		7/10/39	27	**	**					
642665		11/14/39	24	56	88	3 7	7 0	11 8	82	40 min
41—D U		2/15/40	20	56	64	22 0	45 0	51 0	84	
G J —3/20/39										
Ant Resect	143									
7/10/39										
(6)										
Mr G A		6/28/39	15	82	91	12 0				
661081		9/30/39	0	62	78	35 0	79 0	100 0	72	310 min
56—D U		11/7/39	0	40	116	90 0	135 0	384 0	18	145 min
9/18/39	117	4/23/40	66	100	122	12 0	43 8	53 0		

* All patients in this group were operated upon for massive hemorrhage from duodenal ulcers

† Case 1 Table IV

‡ Case 2 Table V

§ Specimens taken 30 minutes after three successive injections of 0.5 mg of histamine

|| This patient has also a stricture of the lower esophagus from 'acid ulceration' of the esophagus

** Operated upon as an emergency for massive hemorrhage threatening life. No preoperative determinations of acid were made

PRE- AND POSTOPERATIVE GASTRIC ACIDITY

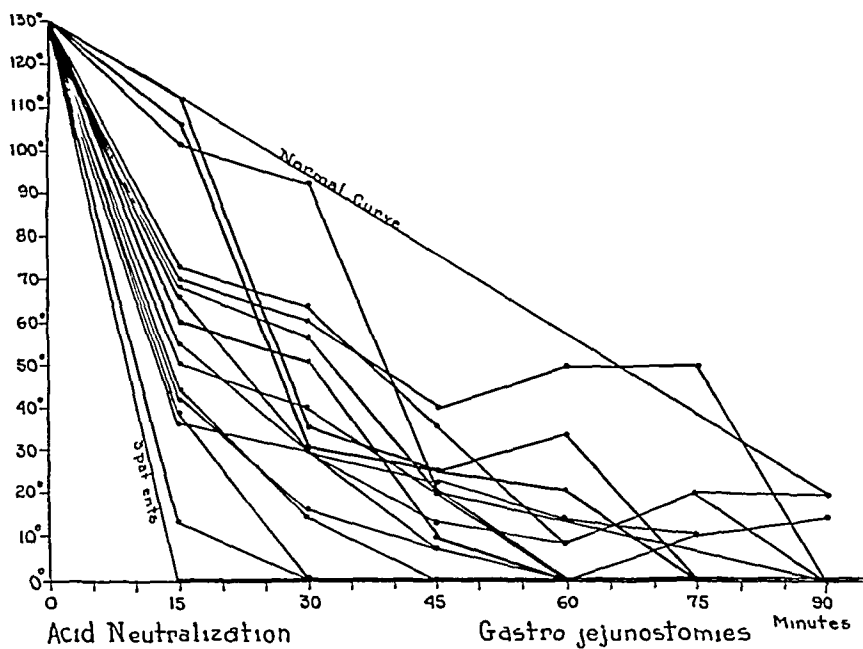


FIG 1—Decreased evacuation time of the stomach occurring after gastrojejunostomy, as indicated by the ability of the stomach to “neutralize” acid. The straight line of the normal curve is that previously employed by Elman (1929)

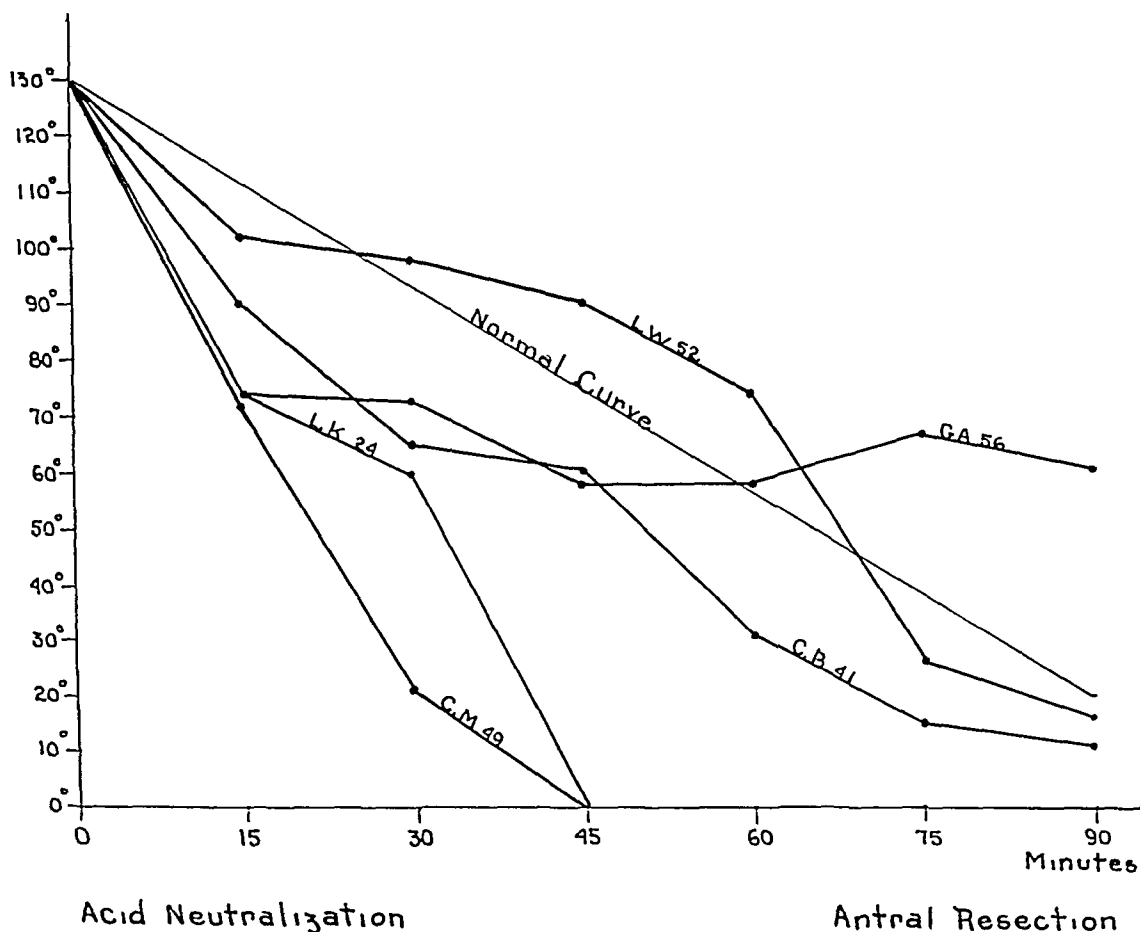


FIG 2—Gastric evacuation time as indicated by acid neutralization after antral resection

TABLE III

EXTENSIVE GASTRIC RESECTION INCLUDING EXCISION OF PYLORUS AND ANTRUM*

Name Hosp No Age—Diag Oper Date	Amount Resected (in sq cm)	Date of Analysis	Fasting Free Acid	Maxi mum Free with Hista mine	Maxi mum Total with Hista mine	Volume of Secre tion ½ hr (in Cc)	Acid Output (Histamine) Mg ½ hr		Acid Neu- tral ze 1 % Acid Loss	Mo tility Emp tying Time —Ba
(1) Mr G T 48237 58—G U 7/3/29		6/15/29 6/24/29 11/9/39	26 26 0		38	11 0	0	15 0	90	
(2) Mrs A K 53599 63—G U 4/21/30		4/10/40	0	0	12	3 2	0	1 4		
(3) Mr A F 604340 42—D U G J—1916 Reop G J—1929 2nd G J—1930 2/29/32		1/25/32 3/14/40	40 0	77 0	93 22	78 0 17 0	219 0 0	264 0 13 6		15 min
(4) Mr M S 625719 44—G U and D U 6/18/35		3/20/34 6/11/35 10/24/39 3/18/40 4/27/40	41 44 0 0 0	37 30 0 84 0†	51 54 36 102 30†	5 0 22 0 9 0 1 1	5 44 0 27 0 0	9 9 28 9 33 0	90	45 min
(5) Mr W R 651309 49—G U 3/24/39	200	5/5/38 4/3/39 5/23/39 6/6/39 10/18/39 2/20/40 4/11/40	20 0 0 0 8 0 0	45 20 0 0 0 0 15†	52 24 8 18 20 16 45†	15 0 8 0 8 8 0 5 0 3 0 2 5	17 5 5 8 0 0 0 0 1 35	35 0 7 0 5 2 2 9 1 75 4 1	93 94 94	10 min
(6) Mr W S 586233 67—G U 1/4/40	178	12/30/39 1/3/40 1/17/40 4/11/40	26 0 0 0	36 14 0 0	63 32 20 37 5	19 5 18 0 12 7 4 4	26 0 9 2 0 0	46 0 21 0 9 0 5 9	54 100 96	5 min
(7) Mr H P 691274 53—G U 2/27/40	295	2/1/40 3/8/40 4/11/40	0 0 0	0 0 0†	14 32 32†	9 0 7 5	0 0	10 5 8 7		9 min
(8) Mrs E F 693430 57—D U and G J U G J—20 yrs ago 3/13/40	201½	3/25/40 4/8/40 4/24/40	0 0 0	0 0† 0	37 5 40† 40	0 15 0 5 3 0	0 0 0	0 19 0 7 4 3		Unable to tol erate 150 cc Stom- ach empties imme- diately

PRE- AND POSTOPERATIVE GASTRIC ACIDITY

TABLE III (Continued)

Name	Amount Resected	Date of Analysis	Fasting Free Acid	Maximum Free with Histamine	Maximum Total with Histamine	Volume of Secretion ½ hr (in Cc)	Acid Output (Histamine) Mg ½ hr		Acid Neutralized % Acid Loss	Motility Emptying Time —Ba
Hosp No	(in sq cm)						Free	Total		
Age—Diag										
Oper Date										
(9)										
Mr F V †		4/11/40	32	72	92	33 0	85 4	111 0		---
694465		4/22/40	0	0	58	7 5	0	16 0		
68 G U										
4/12/40	274									
(10)										
Mr M M		4/14/40	0	94	122	132 0	413 6	539 0		---
694565		2/26/40	0	16	32	15 0	8 7	17 5		
45—prepyloric ulcer										
4/18/40	310									

* Cases 1 2 3 4 5 and 6 had complete terminolateral anastomoses

Cases 7 8 9 and 10 had partial inferior terminolateral anastomoses

Cases 1 3 and 4 had no entero anastomosis All other cases had entero anastomoses

† Specimens taken 30 minutes after three successive injections of 0.5 mg of histamine

‡ This patient had two lesions An ulcer on the lesser curvature and a small carcinoma in the pyloric region The lesions were definitely independent of one another

§ Area determined after the specimen had been in the refrigerator for a few hours—this measurement therefore does not take into account the contraction that occurred Patient operated upon as an emergency for acute massive hemorrhage from gastrojejunal ulcer—consequently no preoperative determinations of gastric acidity

patient in this group (Case 4) has been achlorhydric, even to histamine stimulation After three doses of 0.5 mg of histamine given consecutively over half-hour intervals, however, free hydrochloric acid appeared in the gastric secretion None of the other patients in the group are achlorhydric to histamine, though Case 6 has been achlorhydric, fasting It is apparent that removal of the antrum and pylorus is an unsatisfactory operation to reduce gastric acidity (Fig 2) The rapid emptying observed after gastrojejunostomy was noted also in this group Two of these six patients (Cases 1 and 3) also developed gastrojejunal ulcer which neither patient had after gastrojejunostomy alone With the exception of the patients who developed gastrojejunal ulcer, the others are well The two who developed gastrojejunal ulcer (Cases 1 and 3) will be discussed again under Group V

GROUP III—EXTENSIVE GASTRIC RESECTION INCLUDING EXCISION OF ANTRUM AND PYLORUS

There are ten patients in this group The matter of the size of the resection will be discussed in a separate section All patients in this group have been achlorhydric to histamine at times However, none have been consistently achlorhydric The lapse of time is apparently a factor in establishing achlorhydria (Cases 5 and 6) In the first four cases in the group, the first analysis of gastric acidity after operation made after the lapse of months or years demonstrated achlorhydria regularly We have since learned that it is im-

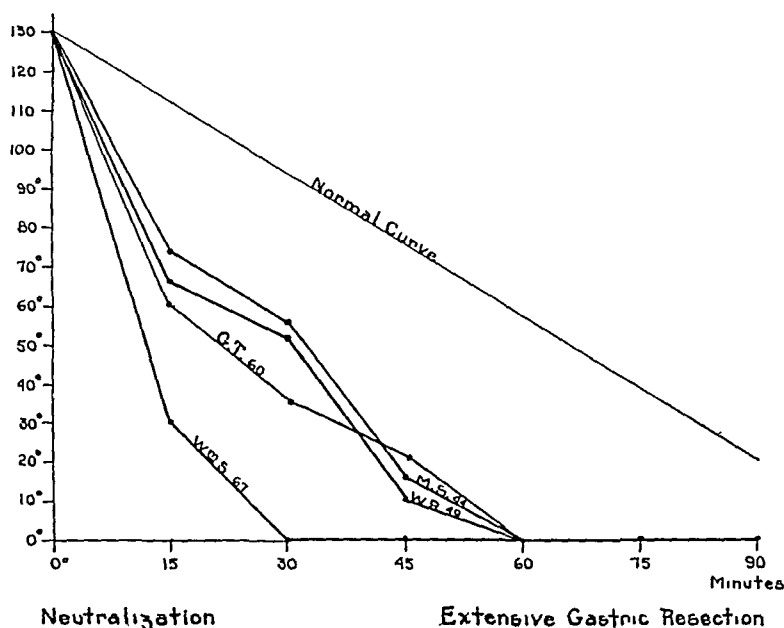


FIG 3—Gastric evacuation time as indicated by acid neutralization after extensive gastric resection (Cases in Group III)

Types of Operative Procedure

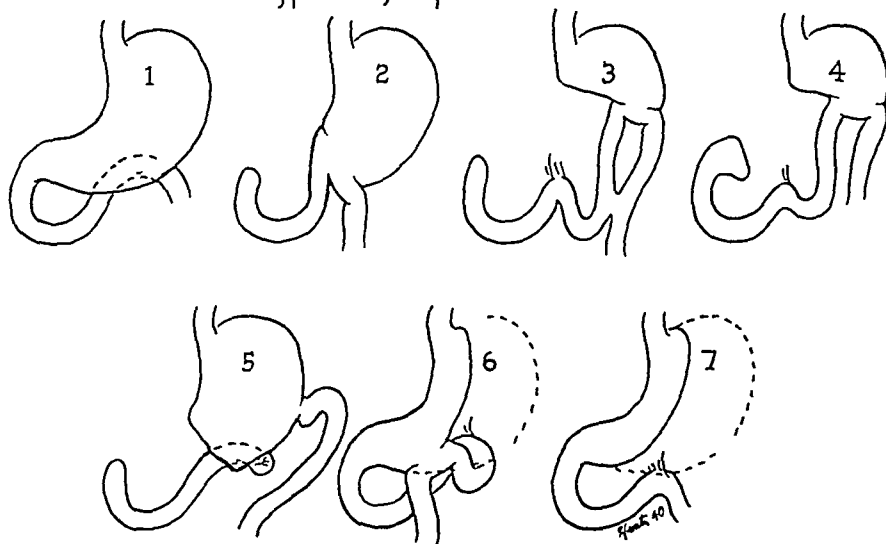


FIG 4—Various types of operative procedures employed in the cases listed in the tables

- 1 Gastrojejunostomy
- 2 Antral resection
- 3 Extensive gastric resection Some patients had entero-anastomosis—others did not
- 4 Extensive gastric resection accompanied by antral exclusion (Finsterer) Some patients had entero anastomosis—others did not
- 5 Schmilinsky procedure providing total intragastric regurgitation
- 6 Tubular resection with gastrojejunostomy leaving pylorus and antrum intact
- 7 Tubular resection without gastrojejunostomy leaving pylorus and antrum intact

PRE- AND POSTOPERATIVE GASTRIC ACIDITY

TABLE IV

EXTENSIVE GASTRIC RESECTION LEAVING THE PYLORUS AND A SMALL SEGMENT
OF THE ANTRUM**Antral Exclusion Operation of Finsterer*

Name	Amount Resected (in sq cm)	Date of Analysis	Fasting Free Acid	Maximum Free Histamine	Maximum Total Histamine	Volume of Secretion ½ hr (in Cc)	Acid Output (Histamine) Mg ½ hr		Acid Neutralized % Acid Loss	Motility Emptying Time —Ba
Hosp No	Age—Diag	Oper Date					Free	Total		
(1)										
Mr P M		4/20/37	14							
658072		6/6/39	0	0	18	10 0	0	6 5	98	10 min
38—D U		2/14/40	0	0	16	3 5	0	2 1	97	
G J —5/1933										
5/13/37										
(2)										
Mrs M B		10/14/39	54							
686389		2/18/40	42							
36—G U		3/7/40	0	0	44	4 3	0	6 9		30 min
2/26/40	225	4/16/40	0	30†	40†	11 0	12 0	16 0		
(3)										
Mr J E		3/2/40	50	64	84	55 0	138 0	168 0		
684691		3/19/40	0	26	32	30 0	28 0	28 6		
38—D U		4/9/40	8	0	20	11 0	0	8 0		120 min
3/8/40	258									
(4)										
Mr E H		2/27/40	0	0	28	2 6	0	2 6	80	
685488		3/27/40	90	122	128	30 0	124 0	140 0		
40—D U		4/15/40	12	38	58	19 0	26 0	40 2		60 min
4/3/40	301	4/22/40	0	56	144	2 6	5 3	13 6		
(5)										
Mr C S		4/2/40	36	86	94	12 0	37 5	41 0		
694074		4/20/40	0	0	24	11 0	0	9 6		35 min
24—D U		4/22/40	0	17 5	42 5	5 0	3 0	7 8		
4/11/40	244									
(6)										
Mr T B		3/29/40	14							
694134		3/30/40	8							
40—D U		3/31/40	44							
4/15/40	224	4/11/40	93							
		4/15/40	106							
		4/22/40	40	70	100	18 0	46 0	62 0		
		4/26/40	36	72	94	51 0	133 0	174 0		

* Complete terminolateral anastomoses in Cases 1 and 2 Partial inferior terminolateral in the others
Entero anastomoses in all but Case 1

† Specimens taken 30 minutes after three successive injections of 0.5 mg of histamine

portant to make observations beginning early in the recovery period to determine when achlorhydria supervenes. Now, save with employment of triple 0.5 mg doses of histamine, all but the last patient in the series (Case 10) is achlorhydric to the usual 0.5 mg dose of histamine.

The emptying of the stomach in this group, in all instances in which the examination has been made, is very rapid (Fig 3). All patients in the group are symptomatically well. There have been no gastrojejunal ulcers.

GROUP IV—EXTENSIVE GASTRIC EXCISION WITH EXCLUSION OF THE PYLORUS
AND ANTRUM (FINSTERER OPERATION)

This type of operation is indicated particularly in duodenal ulcer complicated by choledochoduodenal fistula, or when there is considerable edematous induration of the duodenum, pylorus and antrum. The admonition, of Finsterer, to leave only a portion of the antrum, lest the acid secreting cells

TABLE V

PATIENTS HAVING THE SCHMILINSKY OPERATION FOR GASTRO-JEJUNAL ULCER

(Provision for Complete Intragastric Regurgitation)

Name	Amount Resected	Date of Analysis	Fasting Free Acid	Maximum Free with Histamine	Maximum Total with Histamine	Volume of Secretion ½ hr (in Cc)	Acid Output (Histamine) Mg ½ hr		Acid Neutralized % Acid Loss	Motility Emptying Time —Ba
(1)							Free	Total		
Mr F F		5/29/34	7	8	16					
627911		4/19/35	16	70	82	67	175 0	198 0		
40—D U		12/31/36	0	0	23					--
G J —1918		9/5/39	0	9	39	12	5 0	26 0		
Ant Resect		3/11/40	0	0	30	16	0	13 0		160 min
4/20/35										
Schmilnsky										
1/8/36										
(2)										
Mr L K *		5/25/38	30							
669044		6/13/38		80	100					
24—D U		4/18/39	52							
G J —2/14/39		5/8/39	0	38	50	9	12 3	16 4		
Ant Resect		5/15/39	31							
2/21/39										
Schmilnsky	110	6/28/39	24							
with excision		8/29/39	0	26	40	15	14 3	22 0		
of a portion of										
fundus										
5/15/39										
(3)										
Mr A S †		9/5/35	69							
641802		4/7/39	27							
35—D U		4/14/39	89							
G J 1/1938		4/24/39	16	22	40	25	20 0	36 5		
Excision of gas	214	5/24/39	32							
trojejunal ul-		6/22/39	0	56	60	6	12 2	13 0		
cer and exclu-		7/15/39	0	42	94	11	16 8	37 6		
sion of greater		9/28/39	5	0	21	52	0	39 9		
curvature										
4/14/39										
Schmilnsky	125									
with excision										
of a portion of										
fundus and										
antrum										
8/14/39										

* Died at home suddenly 9/16/39 four months after the Schmilnsky operation of perforation of a new acute gastroduodenal ulcer in the new stoma. Autopsy courtesy Dr B O Mork Jr Worthington Minn.

† Died in hospital 10/8/39 52 days after the performance of Schmilnsky operation of uncontrollable gastric hemorrhage. A large shallow autolytic ulcer of the stomach was found—gastroduodenal ulcer healed.

of the corpus be allowed to remain behind distal to the site of section and inversion of the stomach, has been observed. The upper site of section remains the same as for the ordinary extensive gastric resection described in Group III.

Though there are only six patients in the entire group, the last four have been operated upon since April 1, 1940. After the findings in Group VI had been reviewed (tubular excision of corpus and fundus with gastrojejunostomy—leaving the antrum intact), it became apparent that the performance of a few Finsterer antial exclusion operations accompanied by extensive resection of the acid secreting area, for duodenal ulcer presenting satisfactory indications for operation, would shed additional enlightenment upon the validity of the Edkins' hypothesis in man. As remarked above, under the discussion in Group III, the time element plays an important rôle in making patients achlorhydric after histamine. The first two patients operated upon in this group are achlorhydric to single doses of histamine. The antial exclusion operation is illustrated, together with the other operative procedures, in Figure 4.

GROUP V—THE SCHMILINSKY OPERATION (PROVISION FOR COMPLETE INTRA-GASTRIC REGURGITATION FOR GASTROJEJUNAL ULCER DEVELOPING AFTER ANTRAL EXCISION)

Three patients have been operated upon according to this plan of operation. The first patient in the group, operated upon now more than four years ago, has done fairly well. It is to be noted that his emptying time with barium is still extraordinarily slow and he has not been consistently achlorhydric to histamine. Symptomatically, he does quite well. He has been referred to already as Case 1 in Group II.

The experience with the other two patients in this group suggests that the operation should never be performed. Neither patient became achlorhydric, and in both instances the termination was disastrous. In Case 2, perforation of an acute gastrojejunal ulcer in the new efferent loop caused death in a few hours—the perforation occurring four months after performance of the Schmilinsky operation. The old gastrojejunal ulcer healed (ref footnote, Table V). The other patient developed a large, shallow gastric ulcer which involved a good portion of the residual stomach, and died of uncontrollable gastric hemorrhage, 52 days after performance of the Schmilinsky operation. The old gastrojejunal ulcer healed. The effect of this operative procedure upon the gastric secretory mechanism will be discussed again below under the heading of "Intragastric Regurgitation."

GROUP VI—TUBULAR EXCISION OF CORPUS AND FUNDUS WITH GASTROJEJUNOSTOMY (LEAVING THE ANTRUM AND PYLORUS INTACT)

This operation, in principle, is the same as that of the Connell fundusectomy, save that a much larger area of the acid secreting area is excised and with the addition of provision for partial intragastric regurgitation of duodenal content by a coincident gastrojejunostomy. There are five patients in this group. All had duodenal ulcer, and two of the group had both duodenal

and gastric ulcer (Cases 3 and 4) All are now achlorhydric to histamine* Several are achlorhydric to triple doses of histamine given subcutaneously It is to be noted, again, that in two patients in this group (Cases 2 and 5) the lapse of time played an important factor in establishing achlorhydria to histamine stimulation It should be noted further that the emptying time in this group of patients was not as rapid as in the patients having extensive gastric resection after the Billroth II pattern of operation with terminolateral anasto-

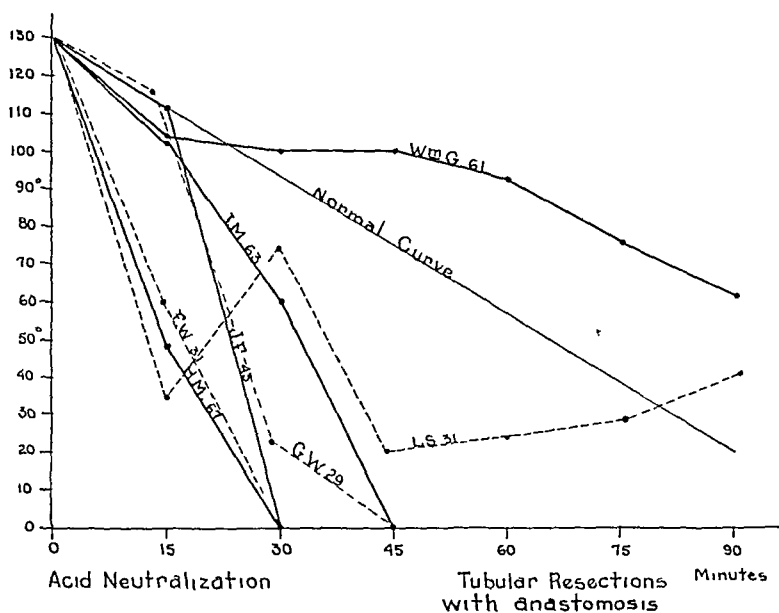


FIG 5 —Gastric evacuation time after tubular resection with gastrojejunostomy, as indicated by the acid neutralization test

mosis with the jejunum No entero-anastomoses were made in this group The amount of gastric tissue excised, paralleled closely that removed in the extensive gastric resections of Groups III and IV All are symptomatically well Roentgenologic examination fails to disclose any evidence of active ulcers In no instance was the ulcer removed Roentgenographically, distortion of the duodenal cap as a result of scarring is still present

GROUP VII—TUBULAR EXCISION OF CORPUS AND FUNDUS WITHOUT GASTROJEJUNOSTOMY (LEAVING THE ANTRUM AND PYLORUS INTACT)

Only three patients have been operated upon by this plan All three were young men with chronic duodenal ulcer causing severe pain and great disability Massive hemorrhage had not occurred in any of the three cases None have been achlorhydric, consistently, fasting or after histamine, though one patient was found to be achlorhydric on one occasion to histamine after operation Significantly, the largest excisions of gastric tissue in the series have been in this group, but without producing achlorhydria The emptying time in all three patients of this group is rapid All are symptomatically well

* Case 5 was not achlorhydric at the time of the most recent examination

PRE- AND POSTOPERATIVE GASTRIC ACIDITY

TABLE VI

PATIENTS HAVING TUBULAR EXCISION OF CORPUS AND FUNDUS WITH GASTROJEJUNOSTOMY

Leaving the Antrum and Pylorus Intact—No Entero-anastomosis

Name	Amount Resected (in sq cm)	Date of Analysis	Fasting Free Acid	Maxi- mum Free with Hista- mine	Maxi- mum Total with Hista- mine	Volume of Secre- tion ½ hr (in Cc)	Acid Output (Histamine) Mg ½ hr	Acid Neu- tralize % Acid Loss	Mo- tility Emp- tying Time —Ba
(1)									
Mr I M		3/2/39	12						
677903		3/12/39	12						190 min
63—D U									
3/24/39	180	3/23/39	22						
		3/24/39	28						
		4/3/39	0	10	22	7 0	2 5	5 6	
		5/18/39	0	20	30				
		8/17/39		16	28				
		2/13/40	0	0	32 5	4 7	0	5 0	
		4/18/40	0	0	17				
(2)									
Mr R S		4/18/39	33	62	74	18 0	22 0	49 0	
658862		4/29/39	0	15	30	10 0	5 4	10 9	
31—D U		8/29/39	0	0	14	15 0	0	7 7	
4/19/39	263	11/14/39	0	0	48	3 0	0	5 0	
		2/6/40	0	0	48	3 1	0	5 3	
(3)									
Mr J F		11/4/37	0	36	40				
663579		3/28/39	0	30	42				
43—G U		5/1/39	0	0	24	5 0	0	4 4	30 min
4/20/39	244	2/20/40	0	0	30	2 0	0	2 18	40 min
		3/8/40	0						96
		4/16/40	0	0*	8*	3 8	0	1 0	
(4)									
Mr H M		5/10/39	35	54	68	24 0	47	60 0	
672813		5/17/39	0	0	14	6 0	0	3 0	
67—G U † and D U									
5/11/39	262								
(5)									
Mr W G		9/5/39	41						
677176		9/14/39	0	108	116	11 0	42	46 0	
61—D U		9/29/39	24	30	60	18 0	19 8	39 4	
9/19/39	245	10/5/39	22	42	64	16 3	25	38 0	
		3/11/40	0	0	30	5 5	0	6 0	70 min
		4/24/40	60	76*	116*	2 6	7 2	10 9	

* Specimens taken 30 minutes after three successive injections of 0.5 mg of histamine

† Gastric ulcer at the esophagogastric juncture on the lesser curvature—benign on biopsy

In Case 1 of this group, the left vagus nerve was cut beside the subdiaphragmatic esophagus. In Case 2, both the vagi were divided below the diaphragm but without any special effect upon gastric secretion.

In young persons, in their twenties, who have chronic duodenal ulcer and present good indications for operation, without a history of massive hemorrhage, this operation has its best indication. Until it is demonstrated definitely

TABLE VII

PATIENTS HAVING TUBULAR EXCISION OF CORPUS AND FUNDUS WITHOUT ANASTOMOSIS

Leaving the Antrum and Pylorus Intact

Name	Amount Resected (in sq cm)	Date of Analysis	Fasting Free Acid	Maxi- mum Free with Hista- mine	Maxi- mum Total with Hista- mine	Volume of Secre- tion ½ hr (in Cc)	Acid Output (Histamine) Mg ½ hr		Acid Neu- tralize % Acid Loss	Moti- lity Emp- tying Time —Ba
(1)										
Mr F W		12/27/37	63							
664758		3/3/39	88	135	143	49 0	244 0	261		
31—D U		10/4/39	70						34	
10/9/39	270	10/6/39	82	114	130	62 0	257 0	293	7	
		10/21/39	0	20	38	46 0	33 0	63	96	
		10/24/39	0							
		11/1/39	—	49	86	14 0	25 0	43	89	8 min
		12/8/39	0	60	90	17 0	37 2	55	85	
		4/10/40	58	92	106	14 0	47 2	54		
(2)										
Mr L S		1/17/40	34	76	94	19 0	55 0	65	42	
688933		1/30/40	0	10	28	25 0	4 5	25	78	
31—D U		3/5/40	26	34	52	19 0	23 5	36	62	6 min
1/18/40	299	4/23/40	7 5	60	100	9 5	20 8	34 6		25 min
(3)										
Mr W G		2/6/40	64	74	88	26 0	68 0	83	77	
691263		2/26/40	0	30	74	24 0	26 0	64		70 min
29—D U		4/9/40	0	0	24	4 5	0	4		
2/23/40	359									

that extensive gastric resection performed according to the Billroth II method will insure achlorhydria with regularity, under all circumstances, an operative procedure of this kind will have its place

Comment—A few facts in this study stand out prominently

(1) Extensive gastric resection *per se* does not produce achlorhydria to maximal stimulation (histamine), even when combined with bilateral subdiaphragmatic vagotomy (Group VII)

(2) Extensive gastric resection, when combined with gastrojejunostomy providing opportunity for partial intragastric regurgitation of duodenal content, will produce achlorhydria to maximal stimulation (histamine) usually. The lapse of time is an important factor in the development of such achlorhydria

(3) Excision of the antrum and pylorus (the small or partial gastric resection) fails to make the residual gastric segment achlorhydric to maximal stimulation

(4) Allowing the antrum and pylorus to remain, as is indicated particularly by the cases in Group VI, does not militate against securing an achlorhydric stomach to maximal (histamine) stimulation, granted that an extensive gastric resection of the acid secreting area is performed. The cases in Group IV will, with the lapse of more time, shed additional light upon this important issue

(5) Gastrojejunostomy is not accompanied by achlorhydria to maximal stimulation

(6) The emptying time is decreased considerably in (a) All anastomotic operations upon the stomach, Groups I, II, III and IV, (b) after extensive resection of the stomach without anastomosis (Group VII) When the intragastric regurgitation of the duodenal content is complete, as it is in Group V, the emptying time is prolonged (barium evacuation time)

The Size of the Gastric Resection—The size of the gastric segment excised has been measured carefully in all patients submitted to operation during the past year After excision, the surgical pathologist* tacks the opened specimen on a board under a very slight stretch, which fails to straighten out the rugae of the mucosa and determines the square area, in centimeters, of the excised specimen This measurement, to be certain, is considerably less than the true area of gastric mucosa removed, into which reckoning account must be taken of the area of the multiple gastric rugae

In the antial excision series (Group II), the area of the excised gastric tissue varied between 110 and 143 sq cm, measured as described above—the average for the group was 124 sq cm In Group III, in those instances in which the area of the excised tissue was determined, this measurement varied between 178 and 295 sq cm, the average being 243 sq cm For Group IV, the area of the excised gastric tissue varied between 224 and 301 sq cm, the average being 250 sq cm In Group VI, the amount of excised tissue averaged 283 sq cm In the successive cases in the group, the respective areas of the excised gastric tissue measured 180, 263, 244, 262 and 244 sq cm In the three cases in Group VII, the excised gastric tissue varied between 270 and 359 sq cm—averaging 309 sq cm

A survey of the data in these groups suggests that excision of 200 sq cm, or more, of tissue, from the corporeal and fundic zones of the stomach of average size, when combined with gastrojejunostomy, after a lapse of time of three to six months after performance of the operation, usually results in an achlorhydric residual gastric pouch to histamine (0.5 mg) Some remain achlorhydric after the triple dose described above By dividing the gastric tissue, under scrutiny, into squares and triangles, as illustrated in Figure 6, the surgeon may readily determine, in an approximate manner, the extent of the area to be removed The senior author, who has performed the gastric resections reported here on man, has found that by employing the scheme depicted in Figure 6, he may excise the desired amount of gastric tissue within a margin of error usually not exceeding 5 to 10 per cent The errors of measurement, with the stomach *in situ*, but devascularized for resection and anastomosis, are usually those of underestimation—that is, the excised specimen, when opened up and tacked down as described above, exhibits an area exceeding that determined at operation by 10 to 20 sq cm

In deciding upon the necessary extent of the excision, the surgeon must of course, be guided by the relative size of the stomach When the stomach is large and dilated, it is necessary to remove a correspondingly larger segment

* The writers gratefully acknowledge the helpful interest of Doctor Hebbel, Instructor in Pathology, in many new phases of the problem

than 200 sq cm—which measurement may be suggested as the *minimal* amount to be removed, to secure achlorhydria in the stomach of average size. The senior author has the impression that duodenal ulcers are more likely to have large stomachs than gastric ulcers (excluding, of course, the pyloric ulcer). An ulcer on the lesser curvature causes shortening, frequently with a resultant smaller stomach. Duodenal ulcer, on the contrary, is more likely to be attended by obstruction and gastric enlargement.

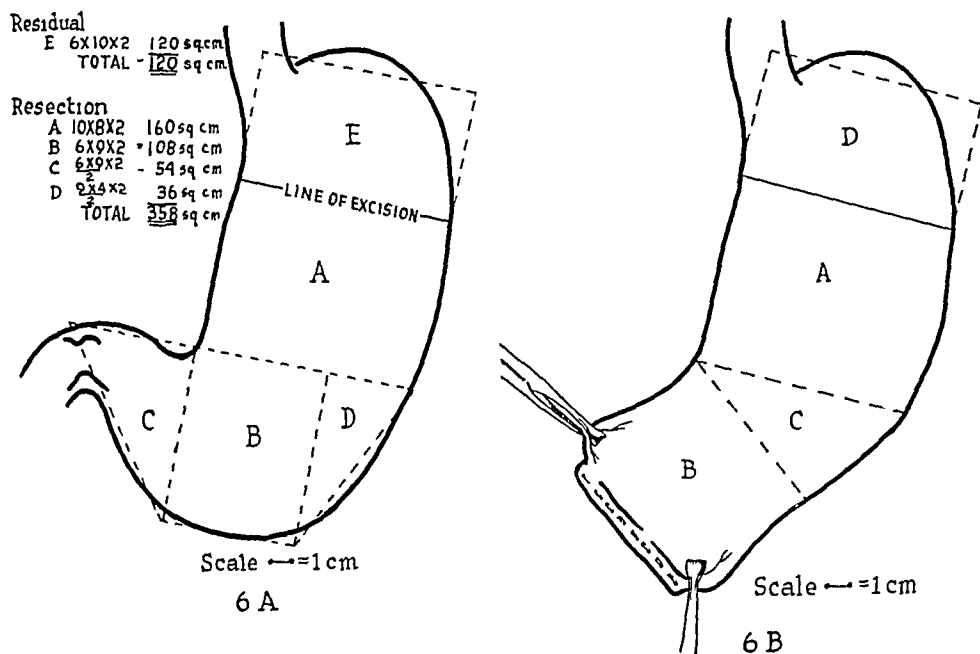


FIG 6—Proposed scheme for determining the surface area of the stomach at operation. It may be done as indicated in 6 A or 6 B, or by some variant thereof.

In order to procure achlorhydria with a high degree of regularity, it is necessary to sacrifice 66 to 80 per cent of the gastric tissue. In the literature, one hears much of small (partial) and extensive (subtotal) resections. Finsterer (1923), who has been an ardent advocate of extensive excision, has insisted the line of division of the stomach should be vertical to the axis of the body. We have enlarged Finsterer's illustration of the proposed segment for removal three times, employing small cardboard plaques cut to pattern and have weighed these out on a fine balance scale. Figure 7 indicates the per cent of the total gastric tissue removed by Finsterer's plan (52 per cent) and confirms the impression, that in allowing so great a length of the greater curvature to remain, it is not likely that the surgeon can excise two-thirds to three-fourths of the stomach. In the diagram, indicating the manner in which the gastric tissue is triangulated and squared-off for excision, is illustrated also the usual extent of the excision as well as the usual size of the residual segment. This type of resection, when accompanied by gastrojejunostomy, is, in the course of a few months, likely to be accompanied by achlorhydria even to histamine stimulation. We have no case with total anacidity. In Case 5

in Group III, at least 95 per cent of the stomach was removed, the lesion being at the esophagogastric juncture on the lesser curvature. The lesion which was believed to be carcinoma proved to be benign. Unfortunately only one preoperative gastric analysis was made.

The Rôle of the Stoma in the Production of Achlorhydria—From inspection of the tables it is apparent that extensive gastric resection *per se* cannot produce achlorhydria, nor can gastrojejunostomy alone. A number of years ago, Harvey (1907) examined the gastric mucous membrane in the vicinity of gastro-enterostomy stomata in dogs, some months after performance of the operation. He observed disappearance of parietal cells from the gastric tubules—cells responsible for the secretion of hydrochloric acid. Since gas-

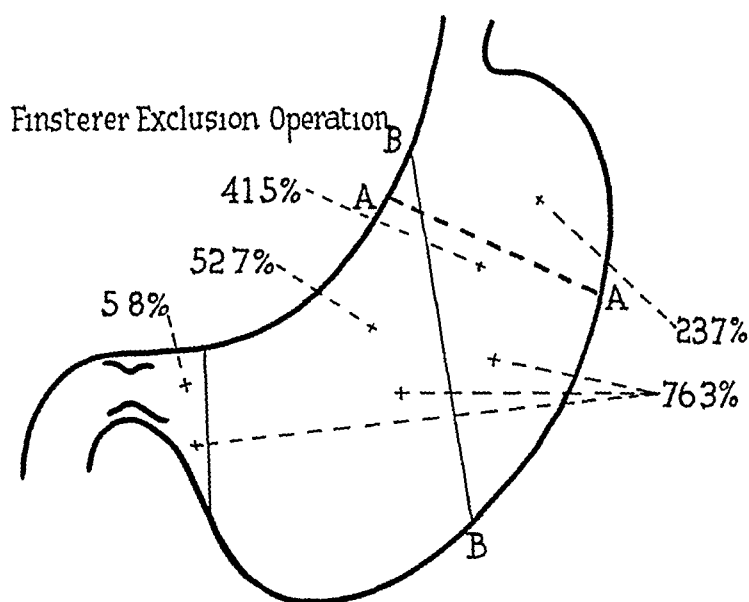


FIG 7—Finsterer's (1923) "subtotal" gastric resection with pyloric exclusion. The actual area removed is 52.7 per cent of the total. By elevating the line of excision on the greater curvature to a higher level, more than 70 per cent of the stomach may be removed.

troscopy has come into quite general use, atrophy and edema of the mucous membrane are not uncommon endoscopic observations upon the operated stomach. Of the present series, the larger number have been subjected to gastrosopic examination. Those findings, however, must await further analysis.

Inasmuch as the time factor appears to be an important item in the establishment of achlorhydria following extensive gastric resection and gastrojejunostomy, it is not unlikely that regurgitated duodenal contents impair the capacity of the parietal cells to secrete hydrochloric acid.

The relatively high total acidities, exhibited by some cases in Tables III and VI, free hydrochloric acid being absent, suggest that hydrochloric acid is either being secreted at a slower rate (most likely) or that with the establishment of the gastrojejunal stoma, more mucus is, through one agency or another (gastric, biliary, duodenal and jejunal), made available to combine with the free acid. It is not unlikely, when ulcer occurs spontaneously in man or is produced experimentally in the cat by intragastric instillation of

acid or the subcutaneous implantation of histamine (see below), that the rapid flow of hydrochloric acid (or secretion as a result of histamine stimulation) over the gastric mucosa washes mucus, the normal buffer for acid, away. When the rate of secretion of hydrochloric acid is slowed up by extensive gastric resection and gastrojejunostomy, enough mucus becomes available to neutralize hydrochloric acid as it is secreted by the gastric glands.

The mechanism by which achlorhydria occurs following excision of gastric tissue and the establishment of gastrojejunostomy, it must be said, is not wholly clear. It is not unlikely that it may be found to be a problem in colloid adsorption chemistry. The manner of adsorption of acid by protein (mucus) in the presence of bile and pancreatic juice on gastric and jejunal mucosal surfaces may have to be studied to solve the problem.

With the cooperation of Dr. Wallace D. Armstrong, associate professor of physiological chemistry, at the University of Minnesota, we recently undertook verification of the values titrated as total acid as being largely hydrochloric acid combined with protein, in patients and dogs in whose gastric contents, after extensive gastric resection and gastrojejunostomy no free hydrochloric acid was found. Much to our surprise, we found considerably less acid in these gastric contents than our titration figures for total acidity (in the absence of free HCl) had suggested. In explanation of this occurrence, Doctor Armstrong says: "The combined acid of gastric juice as determined by the difference between the results of analysis for free acid and total acid has usually been considered to represent, in greatest part, hydrochloric acid combined with protein. It appears very probable that the combined acid should not be interpreted to indicate only hydrochloric acid combined with protein, but also, in addition, the base combining ability of the protein. Proteins, on the alkaline side of their isoelectric point, possess the ability to act as an acid and so combine with base. In general, the base combining power of a protein increases as the p_H of the medium is raised above the isoelectric point of the protein. Since the end-point of the titration of total acid has arbitrarily been fixed at the p_H required to color phenolphthalein (p_H 8.3), it seems certain that a good deal of the alkali used in the titration of total acid is really used in the neutralization of the base combining groups of the protein of the fluid. Thus, the determined value for combined acid represents the alkali required to neutralize the hydrochloric acid combined with proteins plus that needed to neutralize the buffering ability of the protein. The relative proportions of the two will be expected to vary with circumstances depending upon the total hydrochloric acid and protein contents of the fluid."

In this connection, it may not be amiss to discuss briefly the commonly expressed belief that a gastric ulcer becomes achlorhydric more readily after the same type of operative procedure than does duodenal ulcer (Perman, 1935, and Walters, 1937). It is known also that patients with duodenal ulcer tend, in the main, to have higher acid values than gastric ulcer. This may in part be a matter of the size of the stomach as suggested above. However, a gastric ulcer in its typical location, on the mid lesser curvature, with

the frequent attendant indurative edema, radiating several centimeters in each direction into the acid secreting area of the stomach, is likely to injure somewhat the capacity of the stomach to secrete hydrochloric acid

The Amount of Intra-gastric Regurgitation—In this connection, the Schmilnsky operation affords an opportunity to evaluate the effect of total intra-gastric regurgitation of the duodenal content. Up until now, the beneficial effects of intra-gastric regurgitation accompanying anastomotic types of operation, such as gastrojejunostomy, have been attributed to neutralization and dilution of the acid secretions of the stomach. From the few experiences reported here with the Schmilnsky procedure, it is apparent that it is a highly undesirable type of operation. In this connection, it is to be remembered that McCann reported, in 1929, the development of ulcers at the new gastric outlet in 80 per cent of a series of 26 dogs, when the total duodenal secretions were drained back into the gastric fundus. Ivy and Fauley (1931), Weiss, Graves and Gurinarian (1932), and Graves (1935) repeated the McCann experiment, draining the duodenal secretions back, however, into the gastric antrum instead of into the fundus as McCann did. Except for Ivy and Fauley, who noted the occurrence of gastrojejunal ulcers twice at the new gastric outlet, no ulcers were obtained by the other observers. Maier and Grossman (1937) repeated the McCann experiment very much in the manner that McCann performed it initially, but only two dogs out of 12 developed gastrojejunal ulcers. We, too, have eight dogs with the McCann application of the Schmilnsky procedure, in four animals the duodenal content was drained back into the fundus, and in the remaining four into the antrum. All appear well. Four (two of each) have been reexplored after the lapse of at least four months' time in each instance, but no ulcers have been observed. Still our meager but unfortunate experience with the Schmilnsky procedure confirms McCann's observations and stamps total intra-gastric regurgitation of the duodenal contents as undesirable. An additional dog has been kept under observation in the experimental laboratory for more than a year, with the Schmilnsky operation performed as illustrated in Figure 4 (Group V). The pylorus and antrum have been removed and the dog is not achlorhydric despite total intra-gastric regurgitation of the duodenal content (ref. Table VIII).

What may be the explanation of this unusual behavior? To the senior author, only one explanation appears plausible, namely, provision for complete intra-gastric regurgitation protracts, interminably, the second phase (gastric) of gastric secretion and probably intensifies the intestinal phase as well. That is, the acid secreting cells in the residual gastric pouch are constantly stimulated. In time, with the lapse of years, as in Case 1 in Groups II and V, a relative achlorhydria may occur, ultimately, granted that the sequelae of gastric autolysis or perforation of a new gastrojejunal ulcer does not occur in the meanwhile.

The Size of the Stoma and the Question of Entero-anastomosis—The ideal length of the gastrojejunal stoma is not known. In the earlier group

of cases, operated upon after the Billroth II plan of operation, a complete terminolateral (Polya) anastomosis was made. Latterly, an incomplete (inferior) terminolateral (Hofmeister) anastomosis 5 cm in length has been made. In a number of these an entero-anastomosis has been made also. The results of the Schmilinsky procedure suggest, quite definitely, that complete intragastric regurgitation is an undesirable feature. In the main, the large stomata (complete terminolateral anastomosis) empty unusually rapidly ("dumping stomachs"). Whether there is more or less intragastric regurgitation with a large or small stoma is difficult to ascertain definitely.

TABLE VIII

GASTRIC ACIDITY IN DOG'S STOMACH AFTER ESTABLISHMENT OF COMPLETE INTRAGASTRIC REGURGITATION OF DUODENAL CONTENT INTO THE FUNDUS

Schmilinsky Operation

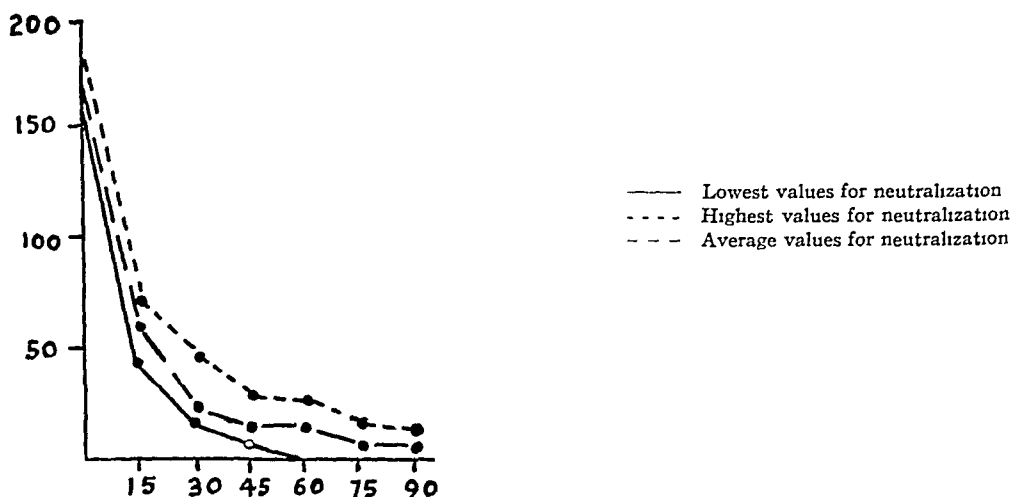
Dog No. 3—Blackie

Procedures and Dates

Antral resection 3/20/39

Duodenogastrostomy 5/17/39
(Schmilinsky)

Dates of Analysis	Fasting Free Acid	Alcohol Free Acid	Histamine Free Acid			Histamine Total Acid			Milligrams HCl with Histamine (Average)	
			Max	Av	Min	Max	Av	Min	Free	Total
4/11/39	0	12		73			88		113.4	138.0
4/12/39	0	11		24			104		17.6	76.0
4/13/39	0	23		24			48		12.2	24.4
4/24/39	0	25.5		34			58		17.45	12.8
2/14/40	0	0	62	32	0	86	62	50	31.5	60.4
2/15/40	0	0	14	4	0	57	46	40	5.6	18.6
4/25/40	0	12	56	37	0	64	44	10	26.8	32.3



Dr George S. Bergh, of this department, and Drs Curtis Nessa and Solveig Bergh, of the Department of Roentgenology, have studied intragastric

regurgitation occurring through gastrojejunostomy stomata by injecting barium and phenolsulphonphthalein in small amounts through a duodenal tube, the tip of which lies well into the duodenum. The amounts of intragastric regurgitation are variable. In the main, regurgitation to the extent of 33 per cent is common in the supine position—a figure which is considerably larger than when the patient stands erect.

In the antral excisions (Group II—six cases) a complete terminolateral anastomosis was made in all instances, achlorhydria to histamine (maximal) stimulation in this group was rare. In the extensive resections (Group III—ten cases) a complete terminolateral anastomosis was made in six patients and an entero-anastomosis was made also six times in four of the patients with incomplete terminolateral anastomosis and in two of the others. In the antral exclusions (Group IV—six cases) complete terminolateral anastomosis was made only twice and an entero-anastomosis was made in five instances. In the tubular resections (Group VI—five cases) no entero-anastomoses were made.

It is difficult to draw any pertinent conclusions from the gastric acidities exhibited by these variants in the operative procedure. Yet it does appear that an entero-anastomosis, if small (3.5 to 4 cm. in length) and placed near the gastrojejunal stoma, may be a helpful procedure, in that, while permitting intragastric regurgitation, it prevents undue prolongation of the gastric phase of gastric secretion by reducing the amount of the duodenal content regurgitated into the stomach. It seems worth while to determine the validity of this premise. It is to be understood clearly, however, that these latter remarks have *no meaning* for any other operation than extensive gastric resection, of the extent herein described.

Gastrojejunal Ulcer—Bergh, Hay and Trach found in studying 138 patients having gastrojejunostomy, available for examination in the University Out-Patient Clinic, that 14 of the group had gastrojejunal ulcer (10.1 per cent). However, only 100 of the group had their gastrojejunostomy operation performed at the University Hospital, five of these had gastrojejunal ulcer (5 per cent). Yet others in the group may still develop gastrojejunal ulcer. Case 8 in Group III, upon whom emergency operation was performed for massive gastric hemorrhage, developed gastrojejunal ulcer (the cause of the bleeding) 20 years after gastrojejunostomy for obstructive duodenal ulcer*. In the experience of Church and Hinton (1940), gastrojejunal ulcer is a far more common sequel to gastrojejunostomy than is generally believed.

Two of the six patients in Group II (these patients appear again in Group V, Cases 1 and 2) with excision of antrum and pylorus developed gastrojejunal ulcer (33 per cent). Klein and his associates (1933) have reported previously an incidence of gastrojejunal ulcer following partial gastric resection of 8.5 per cent, and Lahey and Swinton (1935) noted this as a not infrequent complication of partial gastrectomy for ulcer.

* A patient who developed gastrojejunal ulcer 28 years after gastro-enterostomy was observed recently.

The only other gastrojejunal ulcer in this group of resections is Case 3 in Group V. He came with a gastrojejunal ulcer and when it was excised a portion of the greater curvature was excised, establishing a new gastrojejunostomy stoma in the line of excision. The stomach was extraordinarily large and the excision of 214 sq cm of gastric tissue was inadequate to make the patient achlorhydric.

No recurrent ulcers have been observed in any of the other group of patients.

Starlinger (1930) conducted a written inquiry on the incidence of gastrojejunal or recurrent ulcer after various types of gastric resection. Among 25,121 cases, constituting the basis of his report, only 169 patients were reported as having gastrojejunal or recurrent ulcer (0.7 per cent)—certainly a very conservative estimate (an unsatisfactory manner, however, in which to study its incidence).

Finsterer (1934) admits an incidence of gastrojejunal ulcer of 6.1 per cent after his operation of antral exclusion accompanied by gastric resection. As pointed out above, Finsterer, in insisting on a line of division of the stomach parallel to the vertical axis of the body, must of necessity leave more greater curvature than he is warranted in doing, mindful of the importance of extensive excision of gastric tissue to insure achlorhydria.

TABLE IX

EFFECT OF ANTRAL EXCISION IN STAGLS UPON GASTRIC ACIDITY

(Pavlov Pouch and Residual Stomach)

PREOPERATIVE DETERMINATIONS

Dog No 92—Johnny

	STOMACH SECRETION		
	No. of Determinations—2		
	Degrees of Free Acid		
	Maximum	Average	Minimum
Fasting—1 hr			
Free	48	39	29
Total	55	47	38
Alcohol—½ hr			
Free	80	72	64
Total	87	79	70
Histamine—½ hr			
Free	91	89	87
Total	101	99	90
Histamine—1 hr			
Free	109	106	102
Total	115	113	110
Histamine—1 ½ hr			
Free	69	69	69
Total	76	76	76

(See insert for continuation of Table IX)

Balfour (1928) relates that 26 per cent of gastrojejunal ulcers coming under his observation have achlorhydria. It is very unlikely, however, that any patient with a well authenticated ulcer or gastrojejunal ulcer has a true achlorhydria—that is, is persistently achlorhydric after maximal stimulation with histamine. We have seen no such cases.

The absence of ulcer in patients with pernicious anemia (Kahn, 1937) having achlorhydria, and the absence of stomach ulcers in patients having gastric resection with gastrojejunostomy for cancer, bespeak the importance of acid in the genesis of ulcer, as does also the occurrence of an ulcer in Meckel's diverticulum where only a small fragment of gastric mucosa may cause ulceration with perforation or severe hemorrhage.

Among those who employ gastrojejunostomy for ulcer, the first and most positive indication for the operation is duodenal ulcer with obstruction. In this connection, the experience of those who have practiced the Eiselberg operation of gastrojejunostomy with pyloric exclusion is most important. It is generally conceded that the incidence of gastrojejunal ulcer after the Eiselberg operation is approximately 25 per cent. Only reopening of the pylorus when gastrojejunostomy is undertaken for obstructive ulcer can save the patient from running a similar risk of this dreaded complication. Moreover, Dublin and his associates, of the Metropolitan Life Insurance Company, in speaking of the risks of patients with ulcer, state that recurrent ulcer is the most important factor in mortality of patients who have been operated upon for ulcer.

Graham and Lewis (1935) state that they performed the Devine exclusion operation (transverse division of the stomach at the incisura without excision of gastric tissue) five times, and gastrojejunal ulcer developed at the stoma in all five patients.

Night Secretion—Pavlov believed that fasting was attended by absence of gastric secretion in the dog. Cailson (1916) showed quite definitely, however, for man that the secretion of hydrochloric acid was continuous, and observers since (Pollard and Bloomfield) have come to speak of a basal secretion of hydrochloric acid. Winkelstein believed that secretion of free hydrochloric acid at night occurred only in patients with ulcer and was absent in patients with a normal gastric secretory response without ulcer.

Our findings (Mears and Hay) on this score confirm the previous observations of Cailson, Pollard and Bloomfield, and Hellebrandt, Tepper, Giant and Catherwood. In the main, however, patients with ulcer secrete more hydrochloric acid at night than do patients with normal stomachs. Undoubtedly, this item of night secretion, which will receive but bare mention here, is an important element in the dietary control of ulcer, and probably one of the most important items causing failure of such management. If some manner of suppressing night secretion adequately or controlling it continuously could be evolved, the necessity for surgery in the management of ulcer would diminish considerably. Measures such as suggested by Sand-

weiss (1939) and Brunschwig and his associates (1940) may, some day, make the rôle of the surgeon less prominent in dealing with the ulcer problem.

During the time that the work described above has been under way in the clinic, a broad approach to the ulcer problem has been made in the laboratory. Only a few observations, bearing somewhat intimately upon the questions described above, will be recited here.

Pouch Experiments in the Dog and the Edkins Hypothesis—The validity of the Edkins' hypothesis was put to experimental test in the dog, employing methods very similar to those described previously by Smidt, Portis and Portis, Priestley and Mann, Enderlen and Zukschwerdt, and Shapiro and Beig.

Method—A preliminary assay of the gastric secretory response was first made on the intact stomach. Then, either a Pavlov or a Heidenham pouch was made of the proximal half of the greater curvature of the stomach and

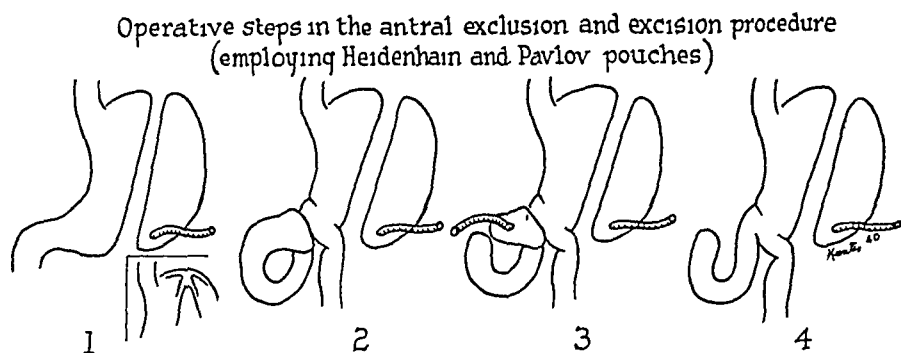


FIG. 8—The various operative steps carried out in trying to evaluate the Edkins hypothesis experimentally by antral excision.

- 1 Establishment of a Heidenham or Pavlov pouch
- 2 Antral exclusion—the line of division being made in the acid-secreting area of the stomach
- 3 Isolation of the antral pouch
- 4 After excision of the antral pouch

the fundus. After complete recovery of the animal, the gastric response in both the residual stomach and the pouch was determined again. Later, an antral exclusion operation was performed, dividing the stomach transversely, the site of section being at or slightly above the incisura. The upper segment of the stomach was then anastomosed to a loop of jejunum. Determinations were made of the gastric secretory response in (1) the residual stomach, (2) the antral pouch, and (3) the Pavlov or Heidenham pouch. Finally, the antral pouch was excised and the effect of its excision noted upon the gastric secretory response in the residual stomach and the Heidenham or Pavlov pouch.

A number of such experiments have been completed. Excision of the antral pouch has been completed only recently in the majority. Nevertheless, our experiments indicate quite definitely that excision of the antrum and pylorus has no effect upon the secretory response in Pavlov or Heidenham pouches in the fundus.

Portis and Portis, and Shapiro and Berg, while noting the absence of effect of antral excision upon the behavior of Pavlov pouches in the fundus of the dog's stomach, described also complete achlorhydria in the residual gastric segment (Portis and Portis), or a distinct lowering of acidity in the residual gastric segment (Shapiro and Berg). However, no special significance was attributed to this occurrence. Yet this is a *most* significant item. Our experiments still fail to indicate whether this is a regurgitation phenomenon (impaired function of acid secreting cells in response to intra-gastric regurgitation of duodenal contents as consequence of gastric resection and gastrojejunostomy) or whether sacrifice of the antrum and pylorus reduces the ability of the residual gastric pouch to sustain the initial capacity for secretion of hydrochloric acid. Reasoning by analogy, having in mind the absence of effect of antral excision upon the secretory capacity of Pavlov or Heidenhain pouches (also see Table X), one might say logically, it must be the regurgitation factor. Factual information can be obtained on this point in the dog which will eliminate the potential errors of apparently sound logic.

Summarizing data are given in Table IX on one such dog after (1) Establishment of a Pavlov pouch, (2) antral exclusion, (3) isolation of

TABLE X

GASTRIC ACIDITY IN LARGE GASTRIC POUCH AND IN SMALL RESIDUAL STOMACH (AFTER GASTRO-JEJUNOSTOMY) FOLLOWING ESTABLISHMENT OF SUBTOTAL GASTRIC POUCH

Dog No. 9—Tony

Procedures and Dates

Subtotal gastric pouch 5/26/39

Residual stomach approx. 20%

Residual Stomach						Subtotal Pouch				
Degrees			Mg HCl in			Degrees			Mg HCl in	
Free Acid	Total Acid	Volume Cc	Free Acid	Total Acid		Free Acid	Total Acid	Volume Cc	Free Acid	Total Acid
5/12/39										
Preoperative Determinations										
Fasting—1 hr	24	46								
Veal broth—1 hr	25	48								
Alcohol—½ hr	66	80								
Histamine—½ hr	76	90								
Histamine—1 hr	16	32								
Histamine—1½ hr	15	33								
3/1/40										
Postoperative Determinations*										
Fasting—1 hr	0	36	2.7	0	3.55	40	72	3.5	5.08	9.13
Veal meal—½ hr	0	56	14	0	28.6	132	146	13	63.0	69.0
Alcohol—½ hr	0	28	10	0	10.2	146	158	15	79.6	86.5
Histamine—½ hr	0	60	17	0	37.2	144	156	13	68.0	74.2
Histamine—1 hr	0	60	20	0	43.8	152	164	12	66.8	72.0
Histamine—1½ hr	0	48	9	0	15.8	152	162	14	77.6	82.8

* In three subsequent determinations the residual stomach was achlorhydric to these stimuli. Achlorhydria in the residual gastric pouch on histamine stimulation since 8/31/39.

antrum as a pouch, and (4) excision of antral pouch and pylorus. Our antral pouches, as we had anticipated, contained, quite uniformly, a fragment of the acid secreting area on the upper end. We wanted to be certain, when the antral pouch was removed, that no antral mucosa remained. The secretion from these antral pouches was, therefore, acid in reaction.

In another dog with a subtotal gastric pouch (isolation of entire stomach save for a small remnant of the fundus), a jejunofundic anastomosis was made. It is to be observed (Table X) that the isolated stomach secretes hydrochloric acid actively. The small residual stomach between esophagus and jejunum, however, has, with the lapse of time, become achlorhydric.

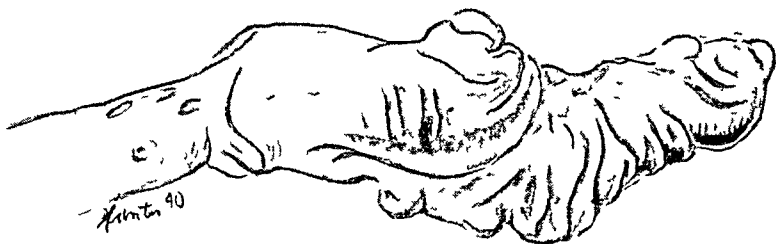


FIG 9.—Drawing of ulcers produced by subcutaneous implantation of histamine in cat

Acid Instillation—Hydrochloric acid (0.4 per cent) was instilled (Walpole) over an interval of 15 to 46 days in four dogs, 82 to 108 cc per hour being allowed to run into the fasting stomach by the drip gravity method through a gastrostomy opening. The instillations were made daily for six and a half to seven hours. The animals were fed late in the day, after the instillation was discontinued. No ulcers occurred in dogs. Samples removed periodically for titration indicated that during the time of acid installation an average acidity of 73 degrees of free hydrochloric acid was maintained in the stomach.

In three of four cats, similarly treated, but given only 40 to 50 per cent as much acid, ulcers were produced in four to 11 days. One cat pulled the gastrostomy tube out on the third day and presented no changes in the stomach, duodenum or esophagus. Ulceration in the cardiac esophagus, fundus, antrum and duodenum was a common finding in the other animals. This finding will be described in greater detail at a later date.

The Production of Ulcers by Subcutaneous Implantation of Histamine in Beeswax—Dr Charles F. Code, Assistant Professor of Physiology at the University of Minnesota, whose studies on histamine assays in body fluids are well known, wished to study the effects of subcutaneous implantation of histamine in beeswax upon the gastric secretory mechanism in dogs. The results of this study will be reported later (Code and Varco). This type of histamine poisoning succeeds in pouring out extraordinary quantities of a

highly concentrated acid. A concentration of 170 degrees (0.62 per cent HCl) has been maintained in the secretion of a Pavlov pouch more than one hour, and a liter of N/10 HCl will be secreted in 24 hours by such a pouch under the powerful stimulus of gradual liberation of histamine.

Histamine in beeswax (20 mg. of the base, equivalent to three times this amount of histamine as ergamine acid phosphate) was implanted into the back muscles at several sites in five cats (Walpole). Ulcers occurred in all in three to nine days—large and small erosions as well as perforating ulcers were observed (Fig. 9).

Antial and Fundic Extracts and Their Effect upon the Gastric Secretory Mechanism—The gastric theory of gastric secretions rests on Edkins' work with pyloric and fundic extracts of gastric mucous membrane and their effect upon the secretory capacity of the cat's stomach. Much work has been done on this phase of the problem by many observers. One of us (Trach), working in collaboration with Dr. C. F. Code, of the Department of Physiology, has prepared histamine-containing and histamine-free extracts of the antial and fundic mucous membrane of both dog and man. In the main, these observations suggest that the histamine-containing extracts, whether from the antrum or the fundus, of both dog and man, exert a stimulating effect upon the secretory capacity of Pavlov and Heidenhain pouches in dogs, as well as upon the intact stomach of the dog. Histamine-free preparations were without effect. These findings will be reported in greater detail at a later date.

Code has determined the histamine content, per gram of antial and fundic mucosa, in both dog and man. He found a larger content of histamine, per unit of mucosal weight, in the fundus for both man and dog. Code also found that the dog's gastric mucosa contains considerably more histamine, per unit of weight, than does man's gastric mucosa. Code's observations on the histamine content of the gastric mucosa of dogs confirm the observations of Gavin, McHenry and Wilson, who found that 80 per cent of the total histamine is to be found in the fundus.

Gastric tissue, it is to be remembered, unlike intestinal mucosa which contains both histamine and histaminase, contains no histaminase. It has already been suggested (Dragstedt, C. A., and associates, 1940) that alcohol mediates its stimulating effect upon gastric secretion by the liberation of histamine. We, too, have noted that alcohol, when instilled into jejunostomy, enterostomy, cecostomy, or colostomy openings in man, exerts a stimulating effect upon gastric secretion in responsive stomachs in man. Similarly, we observed that veal broth instilled into jejunostomies in man excites the gastric secretory mechanism.

Responsiveness of Antial Fundic (Pavlov and Heidenhain) Pouches and the Residual Stomach (after Establishment of Gastro-intestinal Continuity) to Introduction of Alcohol—Sawitsch and Zelony (1913) observed that a greater secretion of hydrochloric acid was obtained from the stomach when food came in contact with antral mucosa. Lim, Ivy and McCarthy

ulcer, should be formulated. Many items enter into consideration which determine choice of operative procedures, and, frequently, standardized indications fail to meet optimally the requirements of a given patient. However, the observations related here have some importance in determining what may be expected reasonably of certain types of operative procedures.

Satisfactory operations for ulcer insure (1) Achlorhydria to maximal stimulation (histamine), and (2) decreased emptying time. Operations which fail to afford real promise of achlorhydria leave too much to chance and hold out too great a risk of gastrojejunal or recurrent ulcer, to stamp them as satisfactory operations to be invoked frequently for the surgical relief of ulcer. Gastrojejunostomy and excision of the pylorus and antrum fall into this class.

Gastrojejunostomy (and probably also, gastroduodenostomy and pyloroplasty) exerts its value through quickening of the gastric evacuation time. Removal of the pylorus and antrum whether by the Billroth I or II plan is probably of no great consequence) is attended by true achlorhydria only occasionally. The virtue of this procedure lies largely, also, in diminution of the emptying time.

Extensive gastric resection when accompanied by gastrojejunostomy is attended usually by achlorhydria to histamine stimulation. When, however, three successive doses of histamine are given, some such gastric pouches, previously achlorhydric, may secrete free hydrochloric acid. True achlorhydria is reported after extensive gastric resection, tubular resection of the corpus and antrum, accompanied by gastrojejunostomy leaving the pylorus and antrum intact), and after the antial exclusion resection (save for the recent cases).

The items necessary to afford real promise of achlorhydria are (1) extensive excision of the acid secreting area, and (2) provision for gastrojejunostomy. Occasionally true achlorhydria follows performance of operation directly, in a number of instances a few months must elapse before achlorhydria occurs. Operations which delay the gastric evacuation time (such as provision for complete intragastric regurgitation) are not likely to be followed by achlorhydria and may, like anastomotic operations which lower gastric evacuation time without lowering gastric acidity, be followed by a high incidence of recurrent ulcer.

It is pointed out that the size of the resection is an important item in determining whether true achlorhydria will occur. The term "subtotal gastric resection"* has been applied by many experienced gastric surgeons, when their own diagrams indicate that they excise in the vicinity of 50 per cent of the total gastric tissue. The surgeon, intent on affording his patient maximal protection against recurrent ulcer, must take more serious account of the amount of gastric tissue which he removes. The minimal amount necessary to excise to afford real promise of achlorhydria is not known. Excision of

* A satisfactory definition of "subtotal" is a little less than all. No resections of less than 80 per cent can be described reasonably as "subtotal."

66 to 80 per cent usually suffices. Whether achlorhydria *per se* carries special risks for the patient remains to be seen.

On the clinical side, the data reported herein appear to indicate that the Edkins hypothesis, of control of the gastric phase of gastric secretion by a pyloric and antial hormone, is invalid. The essence of this proof lies in two occurrences: (1) The consistent production of true achlorhydria in five patients having duodenal ulcer after tubular resection of the corpus and fundus attended by gastrotomy, leaving the pylorus and antrum intact (Group 6). (2) Failure to produce true achlorhydria in patients with excision of the pylorus and antrum (Group 2). Another item bearing directly upon the point in question, but upon which our evidence is not yet complete, is the group of patients in which extensive gastric resection has been performed, but in which the pylorus and a small fragment of the antrum are left (Group 4).

The importance of "night secretion" in this relatively long fasting period is pointed out. It often breaks the effectiveness of dietary control of the ulcer regimen.

On the experimental side, it is indicated that sacrifice of the pylorus and antrum does not diminish the secretory activity of fundic (Pavlov and Heidenhain) pouches. In time, the residual gastric pouch, after antial excision, tends to become achlorhydric. Whether this occurrence is owing largely to impaired gastric secretory capacity, consequent upon gastric resection and provision for intragastric regurgitation, or whether the occurrence is influenced significantly by sacrifice of the antrum, cannot be stated definitely.

On the item of the relative responsiveness of antial and fundic mucosa to the presence of alcohol, our findings are incomplete and inconclusive. Previously recorded data on this score suggest a greater sensitivity of the antral mucosa—an observation which would lend at least partial support for the Edkins' theory of gastric secretion.

The experimental production of ulcer (exogenous) in cats by the introduction of 0.4 per cent acid is reported. (See Walpole et al.) Similarly, the intramuscular implantation of histamine in beeswax (Code) is followed by maximal stimulation of hydrochloric acid secretion, and ulcer can be produced regularly in cats by this method (endogenous). These latter observations lend increased significance to the acid factor in the genesis of ulcer.

Extracts of gastric mucosa, prepared from the stomachs of dog and man, which contain histamine stimulate the secretion of hydrochloric acid in dogs with fundic pouches. Such activity was demonstrated in the extracts prepared from both antral and fundic mucosa. The mucosa of the fundic zone contains more histamine, per unit of weight (per gram), than does antral mucosa (Code) and the dog's gastric mucosa contains more histamine, per unit of weight, than does the gastric mucosa of man.

CONCLUSIONS

(1) Anastomotic operations performed for ulcer fail to produce achlor-

hydria The virtue of such operative procedures is mediated through lessening of the gastric evacuation time

(2) Extensive gastric resection *per se* is not followed by achlorhydria, but when accompanied by gastrojejunostomy, achlorhydria follows, usually with the lapse of time

(3) Provision for complete intragastric regurgitation lengthens the gastric phase of gastric secretion and is undesirable

(4) Excision of the pylorus and antrum in man for ulcer is rarely attended by achlorhydria

(5) Achlorhydria may accompany extensive gastric resection for ulcer, when the pylorus and antrum remain

(6) The Edkins' hypothesis on the clinical side, on the basis of our observations, appears to be invalid On the experimental side, our observations are still incomplete, save that excision of the pylorus and antrum does not decrease the secretory capacity of fundic pouches

(7) The importance of the acid factor in ulcer is emphasized in the occurrence of ulcers in cats after intragastric instillation of 0.4 per cent HCl and after subcutaneous intramuscular implantation of histamine in beeswax

REFERENCES

- ¹ Babkin, B. P. Die sekretorische Tätigkeit der Verdauungsdrüsen. Handbuch der Normalen und Pathologischen Physiologie. A. Bethe, G. Bergmann, G. Embden, and A. Ellinger, Editors. 3, Verdauung und Verdauungsapparat. Berlin, Julius Springer 689-818, 1927
- ² Balfour, D. C. Recurring Ulcers Following Partial Gastrectomy. ANNALS OF SURGERY, 88, 548-553, 1928
- ³ Berg, A. A. The Morality and Late Results of Subtotal Gastrectomy for the Radical Cure of Gastric and Duodenal Ulcer. ANNALS OF SURGERY, 92, 340-359, 1930
- ⁴ Bergh, G. S., Hay, L., and Trach, B. Peptic Ulcer. Staff Meet. Bull., Hospitals of the University of Minnesota, 11, 282-303, March 15, 1940
- ⁵ Bergh, G. S., Nessa, C., and Bergh, S. Unpublished data
- ⁶ Brunshwig, A., Clarke, T. H., Van Prohaska, J., and Schmitz, R. L. A Secretory Depressant in the Achlorhydric Gastric Juice of Patients with Carcinoma of the Stomach. Surg., Gynec. and Obstet., 70, 35-39, 1940
- ⁷ Carlson, A. J. The Control of Hunger in Health and Disease. Chicago, University of Chicago Press, 235, 1916
- ⁸ Church, R. E., and Hinton, J. W. The Results of Gastro-enterostomy in Gastric and Duodenal Ulcers. Surgery, 7, 647-756, 1940
- ⁹ Code, C. F. Unpublished data
- ¹⁰ Code, C. F., and Varco, R. L. Chronic Histamine Action. Proc. Soc. Exper. Biol. and Med., 44, 475-477, 1940
- ¹¹ Connell, F. G. Fundusectomy. A New Principle in the Treatment of Gastric or Duodenal Ulcer. Surg., Gynec. and Obstet., 49, 696-701, 1929
- ^{11a} Dragstedt, C. A., Gray, J. S., Lawton, A. H., and Ramirez de Arellano, M. Does Alcohol Stimulate Gastric Secretion by Liberating Histamine? Proc. Soc. Exper. Biol. and Med., 43, 26-28, Jan., 1940
- ¹² Dublin, L. I., Jimenis, A. O., and Marks, H. H. The Selection of Risks with a History of Gastric or Duodenal Ulcer. The Association of Life Insurance Medical Directors of America. Publications of Metropolitan Life Insurance Company of New York, 1936

- ¹³ Edkins, J S The Chemical Mechanism of Gastric Secretion Jour Physiol, **34**, 133, 1906
- Edkins, J S, and Tweedy, M The Natural Channels of Absorption Evoking the Chemical Mechanism of Gastric Secretion Jour Physiol, **38**, 263, 1908-1909
- ¹⁴ v Eiselsberg, A Zur Ausschaltung inoperablen Pylorusstenosen Arch f klin Chir, **50**, 919-939, 1895
- Idem* Zur Behandlung des Ulcus ventriculi et duodeni Arch f klin Chir, **114**, 539, 1920
- ¹⁵ Elman, R The Behavior of Gastric Acidity in Duodenal Ulcer and Pyloric Obstruction before and after Gastro-Enterostomy Surg, Gynec and Obstet, **49**, 34-42, 1929
- ¹⁶ Elman, R, and MacLeod, J W Neutralization of Gastric Acidity, Ewald Test Meal and X-ray (Barium Meal) Studies in Patients with Duodenal Ulcer, Gastro-Jejunos-tomy and Gastric Resection Am Jour Digest Dis and Nutrit, **2**, 21, 1935
- ¹⁷ Emery, E S Treatment of Peptic Ulcer Complicated by Hypersecretion New Eng-land Jour Med, **210**, 637-641, 1934
- ¹⁸ Enderlein, E, and Zuckschwerdt, L Die Erregung der Magensaftsekretion nach Re-sektion des Antrum-Pylorusteils des Magens Deutsch Ztschr f Chir, **232**, 290, 1931
- ¹⁹ Finsteier, H Local Anaesthesia Methods and Results in Abdominal Surgery Trans by J Burke New York, Rebman Company, 1923
- Idem* Beziehungen zwischen grosse der Magenresektion und Dauerheilung bei der Ulcus-Behandlung Beitr z klin Chir, **147**, 78, 1927
- Idem* Resektion zur Ausschaltung oder Gastro-Enterostomie beim nicht resezierbaren Ulcus duodeni Centralbl f Chir, **61**, 28, 1934
- ²⁰ Friedmann, M Misserfolge bei der sogenannten palliativan Resektion wegen Zwöl-finger Darmgeschwurs Centralbl f Chir, **59**, 1052-1055, 1932
- ²¹ Fromme, A Palliative Resection (Gastroenterostomie oder Palliativresektion [bessere Nomenklatur Resektion zur Ausschaltung, R z A] beim nichtresezier-baren Ulcus duodeni? (63 Tag d deutsch Ges f Chir, Berlin, 1939) Abstracted Internat Abst Surg Surg, Gynec and Obstet, **69**, 565-566, 1939
- ²² Gavin, G, McHenry, E W, and Wilson, M J Histamine in Canine-Gastric Tissues Jour Physiol, **79**, 234-348, 1933
- ²³ Goetze, O Die Motilität und Sekretion des operierten Magens Handbuch der Nor-malen und Pathologischen Physiologie A Bethe, G Bergmann, G Embden, and A Ellinger, Editors **3**, Verdauung und Verdauungsapparat Berlin, Julius Springer, 1199-1239, 1927
- ²⁴ Graham, R R Technical Surgical Procedures for Gastric and Duodenal Ulcer Surg, Gynec and Obstet, **66**, 269-287, 1938
- ²⁵ Graham, R R, and Lewis, F I Jejunal Ulcer J A M A, **104** (Pt 1), 386, 1935
- ²⁶ Graves, A M Combined and Separate Effects of Bile, Pancreatic Secretion, and Trauma in Experimental Peptic Ulcer Arch Surg, **30**, 833 1935
- ²⁷ Haberer, H Chirurgie des Magens Lehrbuch der chirurgie Vienna, Julius Springer, 596-696, 1930
- ²⁸ Harvey, B C H A Study of the Structure of the Gastric Glands of the Dog and the Changes Which They Undergo after Gastro-Enterostomy and Occlusion of the Pylorus Am Jour Anat, **6**, 207, 1907
- ²⁹ Heidenhain, R Untersuchungen über den Bau der Labdrüsen Arch f Mikr Anat, **6**, 368, 1807
- ³⁰ Hellebrandt, F A, Tepper, R H, Grant, H, and Catherwood, R Nocturnal and Diurnal Variations in the Acidity of the Spontaneous Secretion of Gastric Juice Am Jour Digest Dis and Nutrit, **3**, 477-481, 1936
- ³¹ Hoffman, V Die kleine Magenresektion (nach Reichel) beim Ulcus duodeni und ventriculi in dem Ergebnis meiner Nachuntersuchungen Arch f klin Chir, **195**, 312-341, 1939

- ³² Holman, C, and Sandusky, W R Gastric Acidity after Gastro-Enterostomy *Am Jour Med Sci*, 195, 220-230, 1938
- ³³ Ivy, A C The Role of Hormones in Digestion *Physiol Rev*, 10, 282-335, 1930
Idem Discussion of paper by Ivy and Fauley Factors Concerned in Determining Chronicity of Ulcers in Stomach and Upper Intestine, Susceptibility of Jejunum to Ulcer Formation, Effect of Diet on Healing of Acute Gastric Ulcer *Am Jour Surg*, 11, 531, 1931
- ³⁴ Ivy, A C, and Fauley, G B Factors Concerned in Determining Chronicity of Ulcers in Stomach and Upper Intestine, Susceptibility of Jejunum to Ulcer Formation, Effect of Diet on Healing of Acute Gastric Ulcer *Am Jour Surg*, 11, 531, 1931
- ³⁵ Ivy, A C, and Whitlow, J E The Gastrin Theory Put to Physiologic Test *Am Jour Physiol*, 60, 578, 1922
- ³⁶ Kahn, J R Absence of Peptic Ulcer in Pernicious Anemia *Am Jour Med Sci*, 194, 463-466, 1937
- ³⁷ Klein, E Gastric Secretion V Achlorhydria Following Partial Gastrectomy for Ulcer Studies with Histamine and the Transplanted Gastric Pouch *Arch Surg* 30, 162-170, 1935
Idem Gastric Secretion VI The Action of Pilocarpine on Secretions of Transplanted Gastric Pouch without Auerbach's Plexus *Arch Surg*, 30, 277-283, 1935
- ³⁸ Klein, E, Aschner, P W, and Crohn, B B The End-Results of Partial Gastrectomy for Primary Gastric and Duodenal Ulcers Studies in Pre- and Postoperative Gastric Resection *Trans Am Gastro-Enterol Assn*, 36, 197-205, 1933
- ³⁹ Konjetzny, G E Erfahrungen bei der chirurgischen Behandlung des Magen-Duodenumgeschwurs und operativer Misserfolge bei diesem, besonders des Ulcus post-operativum jejunum *Arch f klin Chir*, 182, 685-709, 1935
- ⁴⁰ Konnecke, W Experimentelle Untersuchungen über die Bedeutung des Pylorus-magens für die Ulcusgenese *Arch f klin Chir*, 120, 537-560, 1922
- ⁴¹ Lahey, F H, and Marshall, S F Technique of Subtotal Gastrectomy for Ulcer *Surg, Gynec and Obstet*, 69, 498-507, 1939
- ⁴² Lahey, F H, and Swinton, N W Gastrojejunal Ulcer and Gastrojejunocolic Fistula *Surg, Gynec and Obstet*, 61, 599-612, 1935
- ⁴³ Lewis, Dean Discussion of paper by R R Graham and F I Lewis Jejunal Ulcer *J A M A*, 104, 386-390 (disc p 390), 1935
- ⁴⁴ Lewis, E B Acidity of Gastric Contents after Excision of the Antral Mucosa *Surgery*, 4, 692-699, 1938
- ⁴⁵ Lewisohn, R The Frequency of Gastrojejunal Ulcers *Surg, Gynec and Obstet*, 40, 70-76, 1925
- ⁴⁶ Lim, R K S, Ivy, A C, and McCarthy, J E Contributions to the Physiology of Gastric Secretion I Gastric Secretion by Local (Mechanical and Chemical) Stimulation *Quart Jour Exper Physiol*, 15, 13-53, 1925
- ⁴⁷ London, E S Experimentelle Physiologie und Pathologie der Verdauung (Chymologie) Berlin, Urban and Schwarzenberg, 158, 1925
- ⁴⁸ Lorenz, H, and Schur, H Unsere Erfahrungen über den Wert der Antrumresektion bei der Behandlung des Ulcus pepticum *Arch f klin Chir*, 119, 239-276, 1922
- ⁴⁹ McCann, J C Experimental Peptic Ulcer *Arch Surg*, 19, 600, 1929
- ⁵⁰ Maier, H C, and Grossman, A Relation of Duodenal Regurgitation to the Development of Jejunal Ulcers *Surgery*, 2, 265-274, 1937
- ⁵¹ Mann, F C, and Bollman J L A Symposium Concerned with the Duodenal Factors in the Neutralization of Acid Chyme *Am Jour Digest Dis and Nutrit*, 2, 284-285, 1935
- ⁵² Mann, F C and Williamson, C S The Experimental Production of Peptic Ulcer *ANNALS OF SURGERY*, 77, 409-422, 1923
- ⁵³ Matthews, W B, and Dragstedt, L R The Etiology of Gastric and Duodenal Ulcer *Surg, Gynec and Obstet*, 55, 265-286, 1932
- ⁵⁴ Mears, F B, and Hay, L Unpublished data

- ⁵⁵ Mizoguti, S Experimenteller Beitrag zur Genese des sog postoperativen peptischen Jejunalgeschwurs, insbesondere über die Bedeutung der Acidität des Magensaftes Arch f klin Chir, 195, 118-135, 1939
- ⁵⁶ Ochsner, A, Gage, M, and Hosoi, K Treatment of Peptic Ulcer Based on Physiologic Principles Surg, Gynec and Obstet, 62, (2A), 257-274, 1936
- ⁵⁷ Ogilvie, W H Physiology and the Surgeon Edinburgh Med Jour, 43, 61-83, 1936
Idem Approach to Gastric Surgery II Ulcer of the Stomach Lancet, 2, 295, 1938
- ⁵⁸ Otto, K Die Motilität des Magens nach der Resektion Arch f klin Chir, 197, 448-476, 1939
- ⁵⁹ Pavlov, I P The Work of the Digestive Glands 2nd ed, London, Griffin Company, 1910
- ⁶⁰ Perman, E Surgical Treatment of Gastric and Duodenal Ulcer Acta chir Scandinav, 38-40 (suppl), 1-333, 1935
- ⁶¹ Pollard, W S, and Bloomfield, A L Basal Gastric Secretion in Men Bull Johns Hopkins Hosp, 49, 302-311, 1931
- ⁶² Portis, S A, and Portis, B Effects of Subtotal Gastrectomy on Gastric Secretion Experimental Studies by Aid of a Pavlov Pouch in Dogs J A M A, 86, 836-839, 1926
- ⁶³ Priestley, J T, and Mann, F C Gastric Acidity with Special Reference to the Pars Pylorica and Pyloric Mucosa An Experimental Study Arch Surg, 25, 395-403, 1932
- ⁶⁴ Rieder, W Späteresultate bei ausgedehnter Magenresektion wegen Ulcus ventriculi und duodeni Zentralbl f Chir, 61, 198-203, 1934
- ⁶⁵ Rienhoff, W F, Jr Sympathetic Nerve Block as an Adjunct Anesthesia in Minimal Resection of the Stomach for Peptic Ulcer ANNALS OF SURGERY, 110, 886-906, 1939
- ⁶⁶ St John, F B, Flood, C A, and Gius, J A Effect of Partial Gastrectomy on Acidity and Peptic Activity of Gastric Juice Surgery, 5, 179-184, 1939
- ⁶⁷ Sandweiss, D J, Saltzman, H C, and Farbman, A A Relation of Sex Hormones to Peptic Ulcer Am Jour Digest Dis, 6, 6-12, 1939
- ⁶⁸ Sawitsch, W, and Zelony, G Zur Physiologie des Pylorus Arch f d ges Physiol, 150, 128, 1913
- ⁶⁹ Schmilinsky, H Die Einleitung der gesamten Duodenalsäfte in den Magen (inner Apotheke) Zentralbl f Chir, 45, 416, 1918
- ⁷⁰ Shapiro, P F, and Berg, B N Return of Gastric Acidity after Subtotal Gastrectomy and Double Vagotomy Arch Surg, 28, 160-179, 1934
- ⁷¹ Smidt, H Experimentelle Studien am nach Pawlow isolierten kleinen Magen über die sekretorische Arbeit der Magendrüsen nach den Resektionen Billroth I und II, sowie nach der Pylorusausschaltung nach v Eiselsberg Arch f klin Chir, 125, 26-85, 1923
- ⁷² Smidt, H Über Magensektionen und Magenchemismus Arch f klin Chir, 130, 307-322, 1924
- ⁷³ Starlinger, F Das Rückfallgeschwür nach Magenresektionen wegen primärem Geschwür des, Magens oder Zwölffingerdarms Arch f klin Chir, 160, 409-419, 1930
- ⁷⁴ Steinberg, M E, Brougher, J C, and Vidgoff I J Changes in the Chemistry of the Contents of the Stomach Following Gastric Operations Arch Surg, 15, 749-761, 1927
- ⁷⁵ Straus, A A, Strauss, S, Levitsky, P, Scheman, L, Seidmon, E E, Arens, R A, Meyer, J, and Necheles, H Physiological and Clinical Study of Patients after Subtotal Gastrectomy Am Jour Digest Dis, 4, 32-37, 1937
- ⁷⁶ Tomoda, M, and Aramakı, J Über die Magensaftacidität nach Operationen wegen Magen-Duodenalggeschwür, unter Berücksichtigung der Beziehung zwischen dem Operationserfolge und dem postoperativen Magensaftbefund Arch f klin Chir, 192, 604-617, 1938

- ⁷⁷ Walpole, S H, Varco, R L, Code, C F, and Wangenstein, O H Production of Gastric and Duodenal Ulcers in the Cat by Intramuscular Implantation of Histamine Proc Soc Exper Biol & Med, 44, 619-621, 1940
- ⁷⁸ Walters, W Should Gastric Resection Be Performed for Duodenal Ulcer? Surgery, 2, 759-768, 1937
- ⁷⁹ Wangenstein, O H Aseptic Gastric Resection I A Method of Aseptic Anastomosis Adaptable to Any Segment of the Alimentary Canal (Esophagus, Stomach, Small or Large Intestine), II Including Preliminary Description of Subtotal Excision of the Acid Secreting Area for Ulcer Surg, Gynec and Obstet, 70, 59-70 1940
- ⁸⁰ Weiss, A S, Graves, A, and Gurriaran, G La derivation intragastrique des sucs alcalins duodenaux Compt rend Soc de biol, 109, 916, 1932
- ⁸¹ Wilhelmj, C M, O'Brien, F T, and Hill, F C The Influence of the Pylorus on the Secretion of Acid by the Fundus Am Jour Physiol, 116, 685-696, 1936
- ⁸² Winkelstein, A One Hundred and Sixty-Nine Studies in Gastric Secretion During the Night Am Jour Digest Dis and Nutrit, 1, 778-782, 1935
- ⁸³ Zukschwerdt, L, and Horstmann, H Die operative Behandlung des nicht oder schwer resezierbaren peptischen Geschwures Berechtigung und Anwendung der palliativen Resektionsmethoden fur das Ulcus duodeni (Finsterer), das hochsitzende Geschwur (Madlener) das Ulcus pepticum jejun (Kreuter) Ergebn d Chir u Orthop, 29, 440-510, 1936

DISCUSSION—DR LESTER R DRAGSTEDT (Chicago, Ill) Doctor Wangenstein and his associates deserve our congratulations and thanks for their extensive and painstaking study of the effects of various operative procedures on the physiology of the stomach. It is the kind of information that should have been available many years ago and would have made unnecessary many a surgical experiment on patients with gastric and duodenal ulcer. I do not share the pessimistic view of the ulcer problem expressed by Doctor Ivy in 1931. The vast amount of work done on the lower animals in a large number of laboratories during the past few years has so greatly clarified and extended our knowledge in this field that there are few diseases where our information is more complete.

A typical, chronic progressive ulcer can be produced at will in the dog and the factors necessary for its production are fairly well understood. Pure undiluted gastric juice has the capacity to digest away all living tissue, including the wall of the stomach itself, and an ulcer may be expected whenever opportunity for prolonged contact between such a secretion and the mucosa occurs. The normal stimulus for gastric secretion is the ingestion of food, and this food promptly reduces the acidity and pepsin concentration of the fundus secretion. In many ulcer patients, however, copious secretions of gastric juice occur without the stimulus of food, often during the night, and large amounts of pure gastric juice remain in contact with the gastric and duodenal mucosa for long periods. Solution of the clinical problem would seem to depend upon the discovery of the nature of this abnormal stimulus for gastric secretion.

The interpretation of Doctor Wangenstein that reduction of the acidity of the gastric content following partial gastrectomy, gastrojejunostomy, gastroduodenostomy, and similar procedures, is due to lessening of the gastric phase of secretion through more rapid emptying of the stomach seems well justified by the evidence presented. The new procedures of attempting to reduce the acidity by actual removal of large areas of the acid-secreting fundus are interesting, and it is important that they should be explored by investigators like Doctor Wangenstein and his associates, who are willing also, to study the effects of these operations on gastric physiology.

The fact that subtotal gastrectomy is occasionally necessary to cure the disease does not indicate that this procedure is the solution to the problem, but it is only a confession of our inability in many cases to control the excessive gastric secretion by less radical measures

DR ROSCOE GRAHAM (Toronto, Can) Gastro-enterostomy has been followed by relief of symptoms of duodenal ulcer in spite of the operation. A restudy of a series of our patients has shown of those symptom-free, 47 per cent had malfunctioning stomata

Doctor Wangenstein's contribution is excellent, but it is doubtful whether the relation of acid to recurrent ulceration is still settled. While we have deleted the necessity of operation from the treatment of an uncomplicated duodenal ulcer, we are adding further confusion. Such confusion arises because in reports of operated cases there is not an accurate description of the extent of the resection and the type of reconstruction of the gastro-intestinal tract. Our clinical experience has borne out Doctor Wangenstein's statement—"If we must operate upon patients suffering from complicated duodenal ulcer, such operation should be a radical gastric resection." Doctor Dragstedt says it is an admission of defeat. It is! It is an unphysiologic compromise, which, however, if applied to properly selected cases, produces a happy result, and until we can determine accurately the cause of ulcer, must be an acceptable therapeutic procedure. May we, as a group, in reporting the results of our gastric resections for duodenal ulcer, state accurately the extent of the resection and the method of reconstruction. This, I trust, will avoid many years of confusion and error in arriving at an accurate evaluation of surgical therapy for duodenal ulcer.

DR J. SHELTON HORSLEY (Richmond, Va) Studies of the kind that Doctor Wangenstein and his associates have reported are always interesting. Much gastric surgery has been performed without the proper consideration of the underlying biologic principles. Physiologists have shown that in experimental animals a large portion, often more than 75 per cent, of normal kidney tissue can be removed, if undertaken in different stages, with no apparent permanent interference with the function of the kidney. The same is true of the liver. If more than this maximum amount is excised there may not be enough tissue left to undergo sufficient hyperplasia, and function may, therefore, be permanently affected. It would seem probable that this general law of compensation applies to the stomach, and doubtless accounts for the disappointing late results that follow many operations of so-called fundectomy, or excision of a large quantity of the acid-bearing region of the stomach.

The efficacy of operations on the stomach cannot always be evaluated by the amount of hydrochloric acid in the gastric contents. It is not as simple as that. If, for instance, the estimation of acid in the gastric contents is made before there is opportunity for hyperplasia of the acid-forming cells of the remaining portion of the stomach, naturally the acid will be low or absent. In Doctor Wangenstein's cases there was, I believe, achlorhydria, at some stage, in all of the cases that he reported. Then, too, it is probable that some individuals will have a tendency to compensate for the destruction of the acid-bearing part of the stomach more readily than others. Almost any subtotal resection would leave approximately at least one-fourth of the acid-secreting portion, and, as an analogy between this and the experimental work on the kidneys and liver, it would seem that the remaining portion is capable by hyperplasia of eventually restoring practically the full amount of acid. Other features that enter into the results of gastric operations are the

type of operation performed, and the portion of the intestinal tract into which the gastric contents empty. If, for instance, a Billroth II type of operation is undertaken and an entero-enterostomy performed, much of the alkaline contents of the duodenum is diverted and does not reach the gastric anastomosis. This is, in a sense, the duodenal drainage of Mann and Williamson, which has been found experimentally to result in an ulcer at the site of the anastomosis in almost every instance. Of course the entero-enterostomy does not necessarily drain off all of the alkaline contents, so that the analogy is not complete, but it, at least, takes away some of it and so weakens the resistance of the gastric anastomosis to the acid that is left.

It has been shown by physiologists that the sensitivity of the intestinal mucosa to the acid of the stomach increases from the duodenum down to and including the large intestine. The duodenum ulcerates more frequently because it bears the first brunt of the impact of the acid from the stomach, but an anastomosis with the jejunum, even when there is no entero-enterostomy, entails a greater probability of ulceration from the acid of the stomach than would occur with the same amount of gastric acid emptying into the duodenum.

DR OWEN H. WANGENSTEEN (Minneapolis, Minn., closing). In my presentation, I had no opportunity to allude to the experimental production of ulcer. During the past year, my colleagues and I, with the cooperation of Dr. C. F. Code, Assistant Professor of Physiology, have been exploring some phases of this problem. The daily instillation of 0.4 per cent hydrochloric acid in fairly large amounts over a period of some hours into the stomach of the dog was not followed by the occurrence of ulcer. When, however, similar instillations, but in less amounts, were made into the stomachs of cats, ulcers were produced quite uniformly. Employing a suggestion of Doctor Code that histamine be embedded in beeswax, to permit constant liberation of the histamine, and implanted intramuscularly, ulcers were uniformly produced in cats as well as in the two dogs upon which the experiment has been tried to date. Doctors Cole and Varco have studied the effect of such gradual liberation of histamine upon the secretory capacity of gastric pouches. The effect is profound, high concentrations of hydrochloric acid (0.6 per cent) being poured out in large amounts. I have the impression that we may be able to produce ulcer experimentally by this method in every animal whose stomach secretes hydrochloric acid. We propose to probe this problem further. For therapeutic reasons, it is most important to know whether acid is *the* factor or only *an important* factor in the spontaneous occurrence of ulcer in man.

Mind you it takes only a little wisp of actively secreting gastric mucosa to produce an ulcer. We need only recall what may happen in Meckel's diverticulum, where a bit of gastric mucosa, no larger in area than the thumbnail, may produce hemorrhage or perforation, as is seen more frequently in duodenal or gastric ulcer.

Doctor Horsley referred to the regeneration of gastric mucosa. The regenerative property and capacity of gastric mucosa is well known. When I stated that we removed *by measurement* 66 to 80 per cent of the stomach I admit freely that this measurement probably does not constitute this same fraction of the gastric mucosa. As you know, the mucosa of the upper portion of the stomach is considerably more rugated than the antral portion. When at operation one leaves a small residual gastric pouch which would hold approximately four ounces of fluid (120 cc.) and a few months later, one sees that small residual gastric pouch expanded into a stomach of much

larger proportions, I like to think that the following has happened. Smooth muscle has an enormous capacity for adjusting itself to various degrees of stretch (one need think only of what happens quite normally in the stomach, bowel and bladder), the small residual gastric pouch, even in the absence of obstruction, enlarges to the extent that the mucosa and submucosa will permit the smooth muscle of the stomach to stretch.

So that whereas excision of the amount of stomach described in this presentation appears large, it is to be remembered that the same percentage of the gastric mucosa is not sacrificed.

Patients who have been achlorhydric to histamine, persistently during the early months after operation, have not in our experience exhibited free hydrochloric acid later. The use of continuous suction rather than intermittent aspiration diminishes the possibility of not getting *true* acid values from the gastric juice. Even with the employment of suction it is clear that all the gastric juice cannot be aspirated—hence the weakness of single aspirations.

It is interesting that provision for *some* intragastric regurgitation must be made to produce achlorhydria to histamine stimulation after gastric resection. It would appear that total intragastric regurgitation of the duodenal content is undesirable. *How much* intragastric regurgitation is optimal is not yet apparent. It may prove that the intragastric regurgitation which an ordinary stoma provides is optimal. We have been exploring this query in part by adding entero-anastomoses to some of the extensive gastric resections. An advantage of entero-anastomosis is that it does away with the mechanical derangements at the stoma after gastrojejunal anastomosis—disturbances which are familiar to everyone. I must emphasize, however, that I do not suggest that entero-anastomosis be performed in the ordinary small gastric resection. My colleagues and I do not feel that our findings should be interpreted as indications for choice of operative procedure. What we do mean to point out is what the surgeon may reasonably anticipate from alternative types of operation.

It is extraordinarily interesting that the residual stomach may become persistently achlorhydric to histamine stimulation after gastric resection and gastrojejunal anastomosis of the extent which I have described for, after all, a sizable fragment of gastric mucosa remains still. Dr. Maurice Visscher, Professor of Physiology, with whom I have had many profitable discussions upon the ulcer problem, asked if it was reasonable to believe that one could make the stomach achlorhydric to maximal stimulation (histamine) as long as gastric mucosa remained. It appears that we can.

The surgeon, when operating for ulcer, must be studious in his effort not to inflict upon the patient a worse disorder than that with which the patient came to him. The operation which fails to reduce gastric acidity leaves a great deal to chance and invites the possibility of a recurrent ulcer.

DIAGNOSIS AND SURGICAL MANAGEMENT OF LEIOMYOMATA AND LEIOMYOSARCOMATA OF THE STOMACH*

FRANK H LAHEY, M D

AND

BENTLEY P COLCOCK, M D

BOSTON, MASS

DEPARTMENT OF SURGERY, THE LAHEY CLINIC

AS POINTED OUT by Sworn and Cooper, leiomyomata, said by Boyd (1938) to be the commonest benign tumors of the stomach, receive scant attention in most text-books and are referred to by Romanis and Mitchiner (1937) as usually causing no symptoms whatsoever. In a review of the



FIG 1—Case 1 Roentgenogram of the stomach showing the defect

literature of benign tumors of the stomach, Minnes and Geschickter found that leiomyomata formed 36.6 per cent of all benign tumors of the stomach. Two years later, Chaffin noted the increasing incidence of smooth muscle tumors of the stomach, recording 363 cases that had been reported to date,

* Read before the American Surgical Association, St. Louis, Mo., May 12, 3, 1940

and in the same year Collins and Collins placed the incidence of leiomyomata at 39.9 per cent of all gastric benign tumors. In the study of benign tumors of the stomach made by Eliason and Wright, 60 per cent were leiomyomata. The fact that benign tumors of the stomach, in general, are not infrequent is shown by the fact that Rigler and Ericksen, in 6,742 autopsies performed in four years at the University of Minnesota, found benign tumors formed 26 per cent of all gastric neoplasms.

Regarding their etiology little can be definitely proven. It has been stated by more than one writer that unchecked smooth muscle proliferation



FIG. 2—Case 1. Note on the gross specimen the scars of healed ulcerations over the tumor.

during the healing phase of gastric ulcer may be an originating factor in this condition.

The sex incidence of these tumors is about equal—in our seven cases, four men and three women. The average age of 529 reported cases was 53.6 years, in our cases, 44 years.

Rudolf Virchow (1863) was the first to classify gastric leiomyomata pathologically. He divided them into internal (submucous) and external (subserous). That this classification, though crude, has an important bearing on the symptomatology produced by these tumors can readily be seen in the histories in our cases, all of which were intragastric.

There are no definite laboratory findings in these cases except anemia,

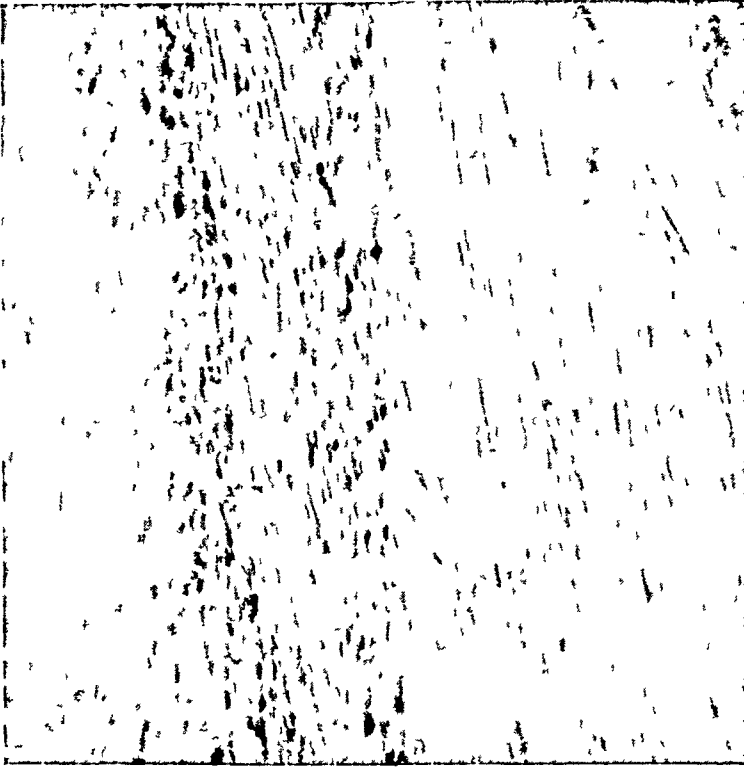


FIG 3—Case 1 Photomicrograph of portion of stomach wall showing infiltrating tumor. At top and bottom, tumor cells are seen in cross section, in central portion of muscularis, in longitudinal section. Cells tend to be spindle shaped. Intercellular substance absent. Malignant tumor, probably atypical leiomyosarcoma ($\times 270$).



FIG 4—Case 2 A recent photograph

and there is no relationship to gastric acidity. The lowest hemoglobin in our cases was 36, the highest 88, and the average 63. The lowest red blood count was 2,200,000, the highest 4,500,000, the average 3,100,000. Reliance in diagnosis must be placed upon the roentgenologic findings, plus an appreciation of the occurrence and clinical importance of these tumors. They are most commonly found in the lower portion of the stomach, and the incidence of involvement of the two curvatures is about equal. Chaffin reports the most characteristic roentgenologic finding as being relatively clear rugae and undisturbed peristalsis in the immediate neighborhood of the tumor. The

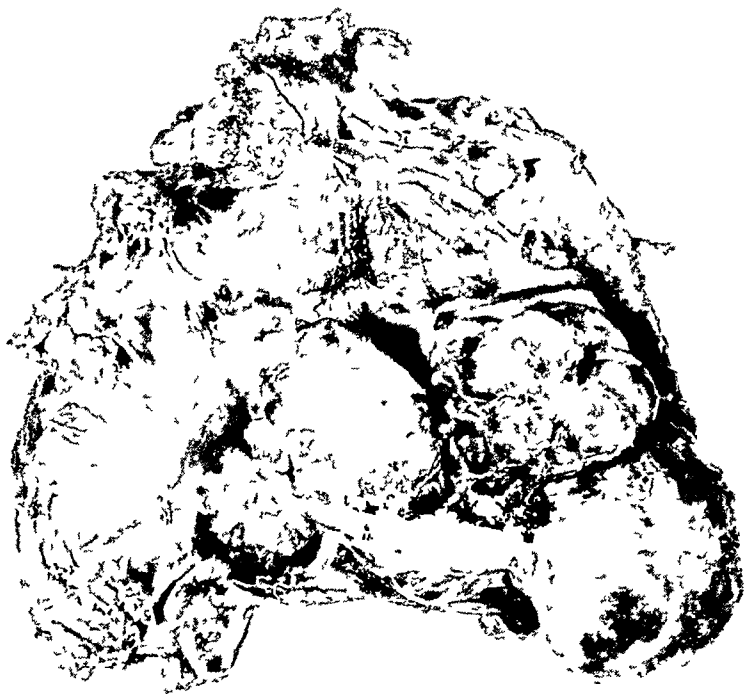


FIG 5—Case 2. A photograph of the entirely removed stomach with the stomach opened showing the leiomyosarcomatous masses occupying most of the stomach.

outline defect made by the more or less spherical tumor was the most common roentgenologic finding in our cases. The pedunculated tumors are, of course, movable on palpation and not infrequently cause pyloric obstruction. Matas has reported a pedunculated leiomyoma acting as a ball valve.

The third most important fact of clinical importance regarding these gastric tumors (the first two being hemorrhage and obstruction) is malignant degeneration. As we review our cases it seems probable that they all originated in a leiomyoma originally benign. The fact that Collins and Collins found 54 recorded cases of malignant leiomyomata of the stomach indicates that malignant change in these benign gastric tumors is probably more common than supposed.

Of seven patients operated upon in our clinic for leiomyomatous tumors

of the stomach, five, or 71 per cent, showed sarcomatous degeneration. This is undoubtedly a high average. (The average hemoglobin in the seven cases, when first seen, was 63 per cent, and the average erythrocyte count 3,100,000.) The average time after the beginning of symptoms (largely hemorrhage) attributable to the tumor when these patients were seen and operated upon was 17 months. Five of the seven patients had had hematemesis or tarry stools: one for three weeks, one for four weeks, one for 18 months, one for four years, and one for 30 months.

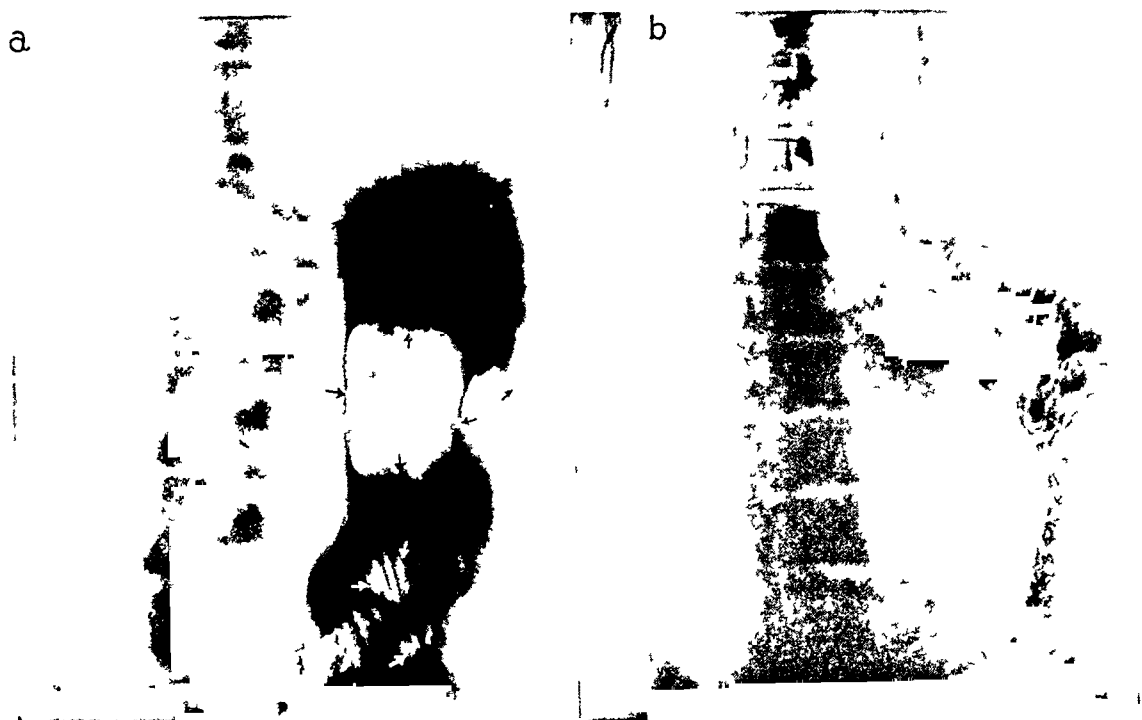


FIG 6—Case 2. (a) Roentgenogram of the stomach showing the tumor masses occupying most of the stomach. (b) A postoperative roentgenogram showing the jejunum anastomosed to the esophagus. Note the long antecolic loop of jejunum without an enteroenterostomy, and how well it functions.

Because of the reported incidence (36 per cent of all benign tumors of the stomach, Minnes and Geschickter) of leiomyomata, because of the high percentage of malignant degeneration (five out of seven in our cases), because of the high grade of secondary anemia present when the patients presented themselves for treatment, and because of the relatively long histories likewise present when these patients first appeared for surgical treatment, it seems desirable to call attention, in a brief and simple way, to this relatively small but important group of gastric tumor cases.

From our experience with this small group of cases and from the reports in the literature, it may reasonably be said that leiomyomata of the stomach are not rare, that the predominating intragastric types tend to become ulcerated on their surfaces (Figs 2, 12 and 15), and to produce hematemesis or melena, that they may or may not produce digestive symptoms, and that they possess real dangers of sarcomatous degeneration. It should be realized that ulceration of the surface and into the substance of these tumors is a

quite common complication with them, and that in any patient with hematemesis or melena the possible presence of an ulcerated leiomyoma should be kept in mind and searched for in gastric roentgenologic examinations to explain gastric bleeding

From the experience with these seven cases, we can say that there is nothing characteristic in these tumors, when they are single and discrete, whereby one may foretell with certainty, either roentgenologically, by gastroscopy, or even on direct visualization, whether or not sarcomatous degeneration has already taken place. When the tumors are multiple and have

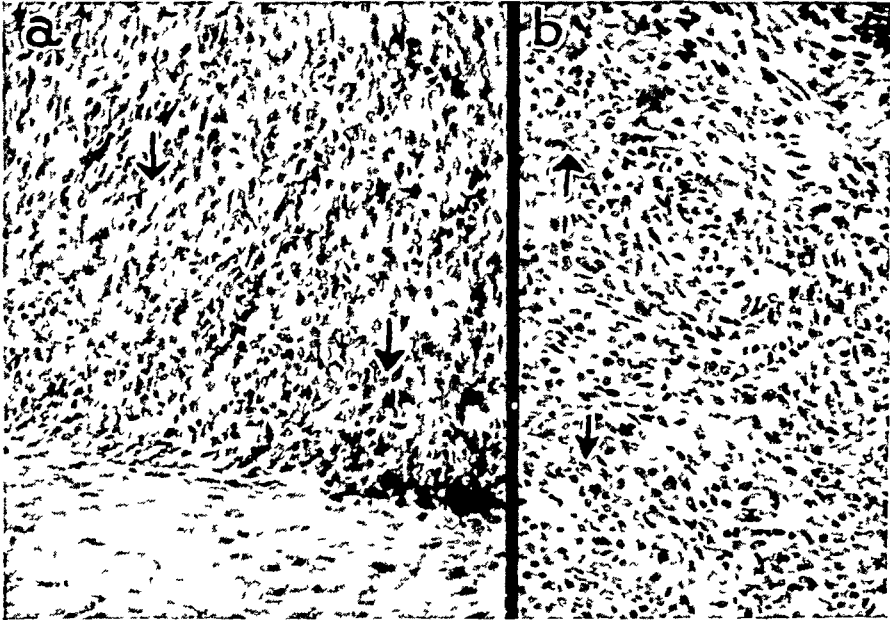


FIG 7—Case 2 (a) Photomicrograph of portion of leiomyosarcoma removed in 1933 showing spindle character of cells and scattered giant cells ($\times 300$) (b) Essentially similar picture. Tumor removed in 1937 showing slightly greater cellularity. Leiomyosarcoma ($\times 300$)

involved the entire stomach, as was the case in the patient submitted to total gastrectomy (Case 2, alive and well now three and one-half years) one can, of course, reasonably assume that sarcomatous degeneration has already taken place, as was the case in this patient

CASE REPORTS^{*}

Case 1—Hosp No 40230. A male, age 39, was first seen at the clinic, May 17, 1934 because of profuse gastric hemorrhages. The first one had occurred a year and one-half previously, at which time he vomited "several quarts" of fresh blood. Two months before admission he had had a second profuse intestinal hemorrhage, and one month before, a third. He had lost 12 pounds and his hemoglobin was 65 per cent. Roentgenograms revealed an egg-sized tumor projecting into the lower portion of his stomach with ulceration on its surface. At operation, a large movable tumor, 8 cm in diameter, was found just proximal to the pylorus, on the greater curvature. Subtotal resection was performed and he made an uneventful convalescence. The pathologic report showed atypical leiomyosarcoma of low malignancy.

* The pathologic diagnoses of the tumors were made by Dr Shields Warren, Pathologist to the New England Baptist and New England Deaconess Hospitals.

GASTRIC LEIOMYOMA AND LEIOMYOSARCOMA

In a report from the patient, dated April 4, 1940, he had had no further hemorrhages, was getting along well, and working every day

Case 2—Hosp No 72221 A female, age 27, had been treated for several years for

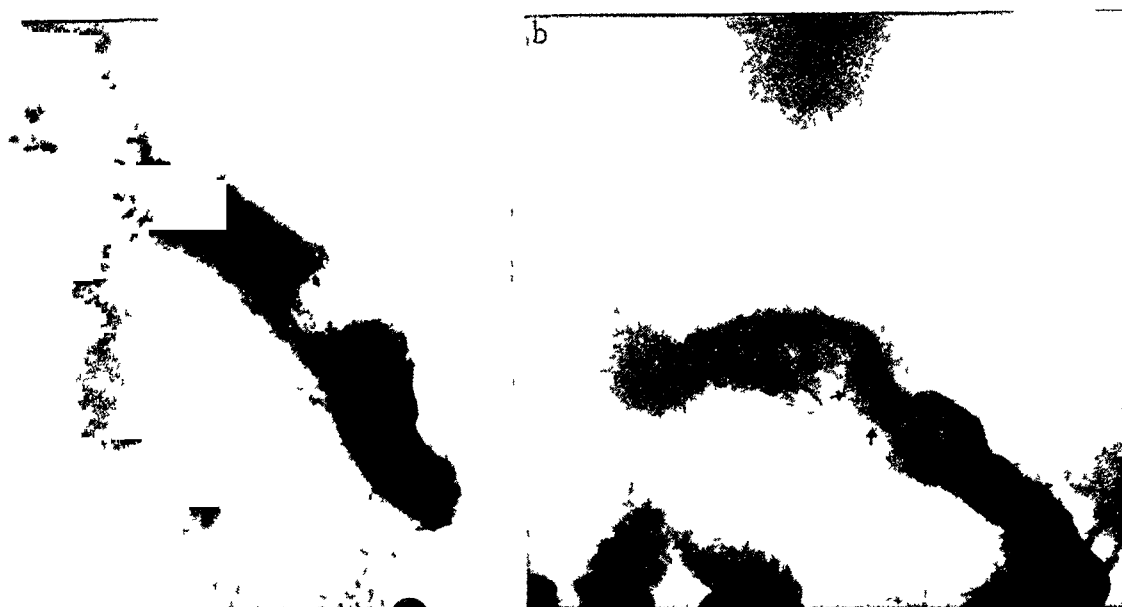


FIG 8—Case 3 (a) Note the typical roentgenographic defect, (b) note the completeness of the outline of the tumor in the roentgenogram This is no guarantee of the absence of malignancy



FIG 9—Case 3 The gross specimen shows the typical intragastric leiomyoma

a secondary anemia of unknown origin Four years before admission she had had a profuse hemorrhage from her mouth associated with tarry stools At that time, December 7 1933 she was operated upon elsewhere and her stomach was found to contain multiple

lobulated tumors along the lesser curvature. The lower group of tumors only were excised. The pathologic report was leiomyoma. Following operation she continued to run a considerable degree of anemia associated with repeated and rather alarming hemorrhages.

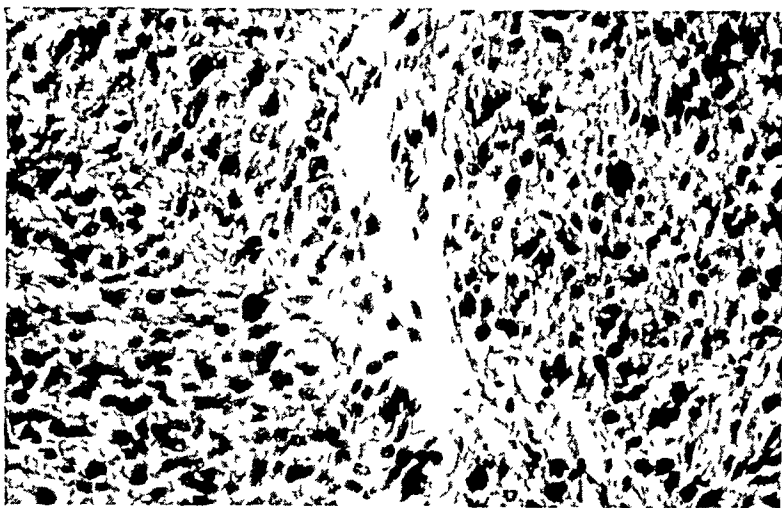


FIG 10—Case 3. Photomicrograph of portion of leiomyoma showing well defined smooth muscle cells with some supporting stroma. Moderate variation in nuclear size. No evidence of malignancy. ($\times 300$)

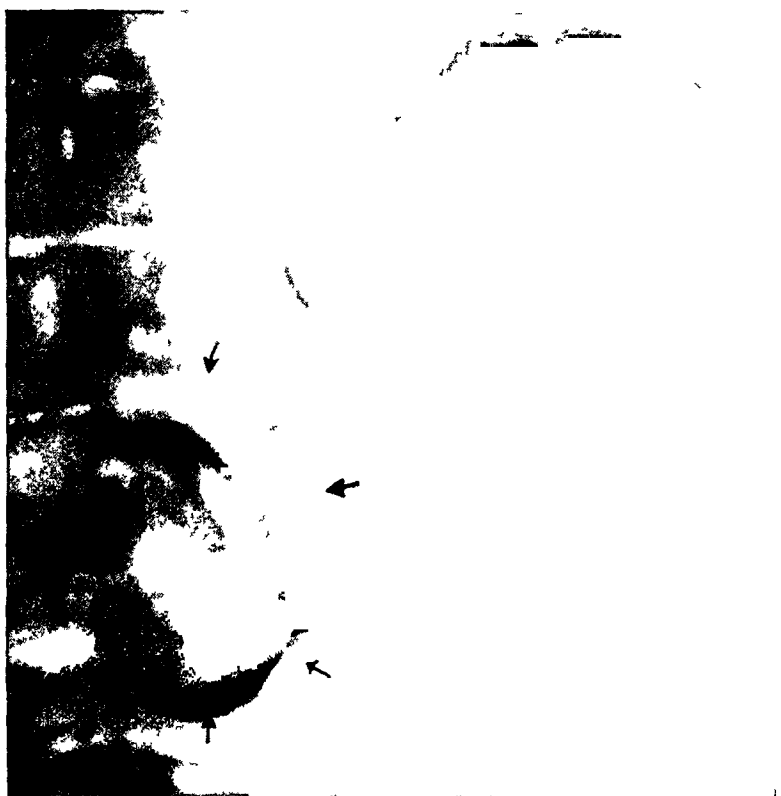


FIG 11—Case 4. Note large gastric defect as shown roentgenographically.

At her admission to the clinic, October 8, 1937, her hemoglobin was 53 per cent, and her red cell count 3,460,000. Roentgenologic examination revealed several intraluminal filling defects in the stomach, occupying most of the cardiac portion of the stomach, the

GASTRIC LEIOMYOMA AND LEIOMYOSARCOMA

largest of which measured 7 cm on the film, and came within one inch of the cardiac end of the esophagus. This finding was verified at operation. Total gastrectomy was performed, October 18, 1937. The pathologic diagnosis was leiomyosarcoma.

This patient reports, April 6, 1940, that she has married in the past year, that she is



FIG 12—Case 4. Note the ulceration over the tumor—a finding present in many of these cases and obviously the explanation of the frequency of hemorrhages in patients with this type of gastric tumor.

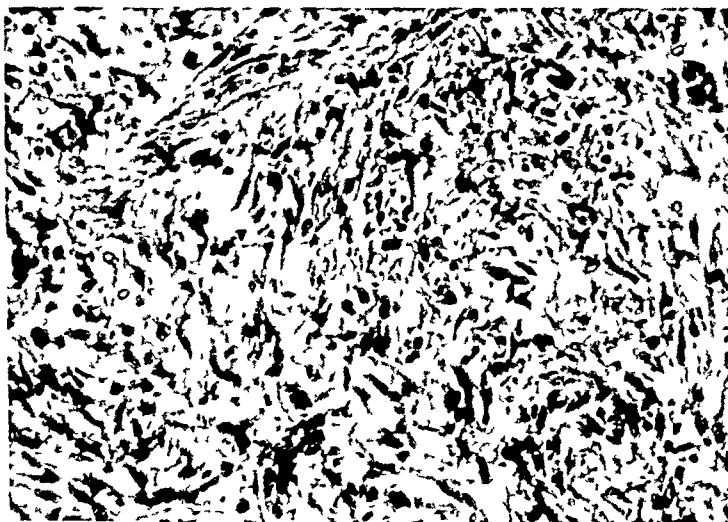


FIG 13—Case 4. Portion of less differentiated part of leiomyosarcoma of low malignancy showing elongated smooth muscle cells with irregular nuclei. Tissue fairly edematous. (×300)

well in every way and maintains her weight and blood picture. She receives iron, liver and hydrochloric acid and pepsin. She eats without difficulty.

Case 3—Hosp No 75739. A male, age 60, came to the clinic February 10, 1938, because of indigestion for 15 years. He had noticed attacks of vertigo and faintness for

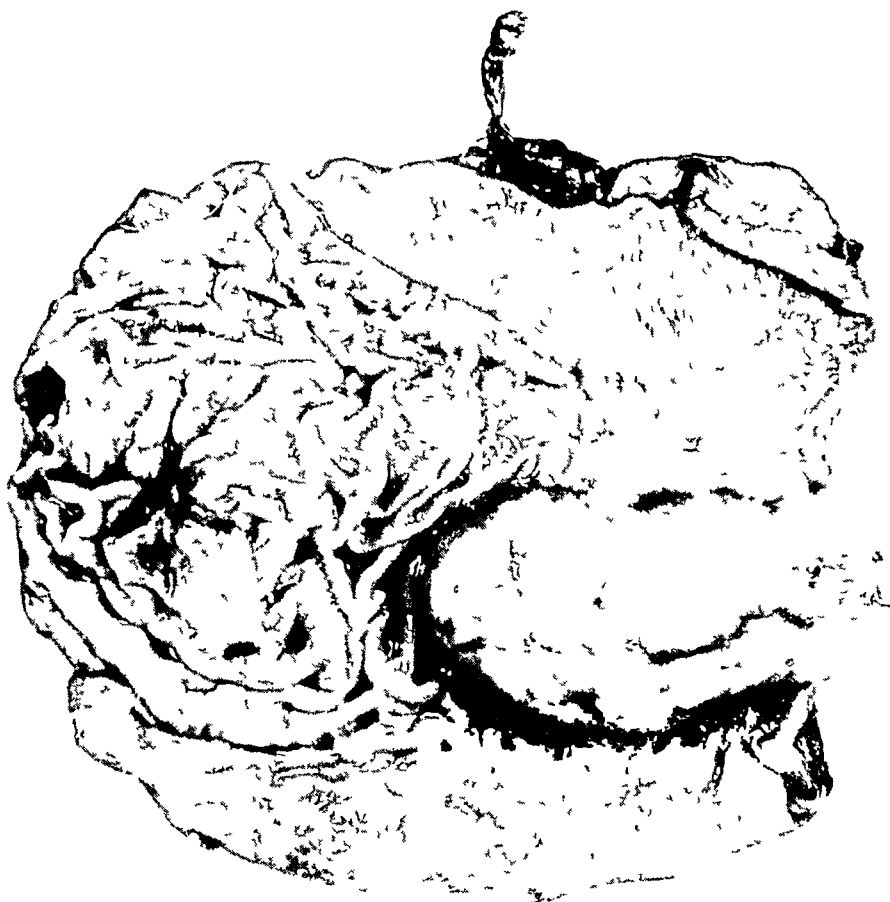
the last six years, accompanied by diarrhea on several occasions. A roentgenogram a year previously had shown a polyp of the stomach. His hemoglobin was 88 per cent, and erythrocyte count 4,480,000. Roentgenologic examination revealed a filling defect in the lesser curvature. The tumor appeared to have a rather broad base. At operation,



FIG. 14.—Case 5. Note the large roentgenographic defect made by the tumor.

May 31, 1938, a circumscribed polypoid mass, 5 cm. in diameter, was found, which projected partly through the serosa of the stomach in the pyloric region. Subtotal gastrectomy was performed. The pathologic report was leiomyoma.

Case 4—Hosp. No. 80367. A male, age 51, was seen at the clinic, June 17, 1938, because he had suddenly begun to pass dark stools three weeks previously. This had continued, and at the time of admission he felt quite weak. His hemoglobin was 72 per cent and his erythrocyte count, 2,176,000. A roentgenogram showed a large filling defect in the pyloric region of the stomach. At operation, June 22, 1938, a large tumor, 10 cm. in diameter, was found just proximal to the pylorus and a subtotal gastrectomy was performed. The pathologic report was leiomyosarcoma.



RIC 1 2 3 4 5 6 7 8 9 10 11 12 13

FIG. 15—Case 5. Note in the gross specimen, the healed scar over the tumor indicating the tendency for these tumors to ulcerate and bleed.



FIG. 16—Case 5. Photomicrograph showing portion of leiomyoma (benign) with well differentiated smooth muscle cells. Note elongated, mature character of the nuclei and fairly orderly arrangement of cells. (×300)

A letter from the patient, dated April 4, 1940, stated that he was well in every way and had had no more hemorrhages. He is maintaining his weight and working regularly.

Case 5—Hosp No 95855. A male, age 40, came to the clinic, May 17, 1939, and stated that he had first noted black stools a year and one-half previously. Nine months ago he had had a severe hemorrhage which forced him to bed for three weeks. In spite of a Sippy diet and ulcer regimen he had had a third hemorrhage three weeks before



FIG 17—Case 6. The gross specimen divided and shown in cross section.

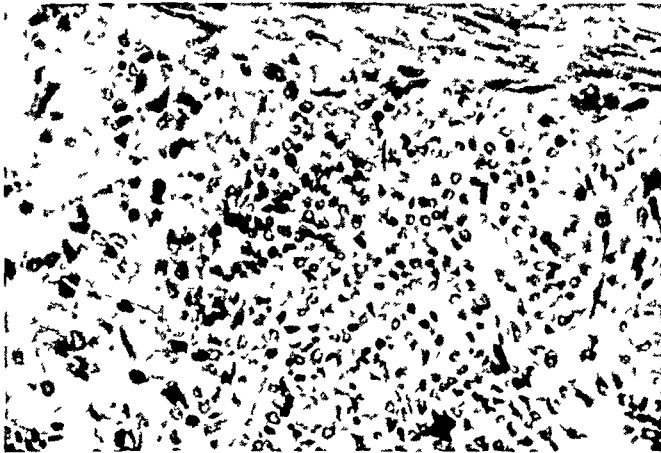


FIG 18—Case 6. Photomicrograph of portion of leiomyosarcoma showing many cells in cross section, some in longitudinal section. Note the large size of some nuclei. Low grade malignancy ($\times 500$).

admission. His hemoglobin was 58 per cent and erythrocytes numbered 3,670,000. Roentgenologic examination revealed a filling defect involving the prepyloric area on the lesser curvature of the stomach. At operation, September 8, 1939, a soft mass, approximately 5 cm in diameter, was found in this region. Subtotal gastrectomy was performed. The pathologic diagnosis was leiomyoma.

The patient reported personally, April 5, 1940, and is well in every way.

Case 6—Hosp No 97271 A female, age 47, came to the clinic, October 3, 1939, stating that four weeks before admission she had suddenly vomited a profuse amount of blood. She was taken to a hospital where she had three more hemorrhages and five transfusions during a period of two weeks. Her hemoglobin was 67 per cent, and erythrocytes numbered 3,410,000. A roentgenogram revealed a large mass in the fundus of the stomach arising from the superior medial wall. At operation, October 6, 1939, a large, freely movable mass was found arising from the cardia near the esophagus. The mass was pedunculated and submucous excision was performed. The pathologic report was leiomyosarcoma of low malignancy.

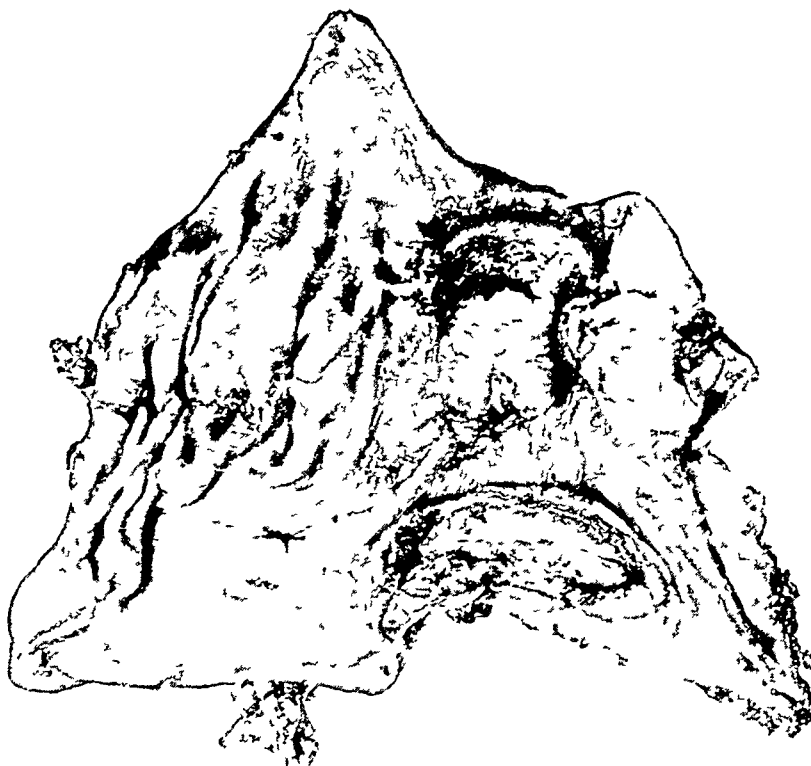


FIG 19—Case 7 The gross specimen shown in the removed portion of the stomach

A report from the patient, April 3, 1940, stated that she had gained 14 pounds, felt quite well and had had no more hemorrhages.

Case 7—Hosp No 310-1 A female, age 45, was seen at the clinic, December 20, 1939, because of persistent anemia and weakness which had been present for two years. Her hemoglobin was 44 per cent, with an erythrocyte count of 3,340,000. Roentgenologic examination revealed a discrete, oval, pedunculated mass lying within the midportion of the antrum. At operation, December 30, 1939, a mass 3 cm in diameter was found within the lumen of the stomach, attached by a broad base, which was considerably indurated. Subtotal gastrectomy was performed. The pathologic report was leiomyosarcoma. She was discharged, January 18, 1940, eating well and wound well healed.

This patient remains well but the operation is so recent that any follow-up report is without value.

In the light of our experience with sarcomatous degeneration in these tumors we do not believe that they should be treated by local removal but rather by high subtotal gastrectomy in order that the tumor and its base, together with a wide margin of gastric wall about it, may be included in the

removal This procedure was employed in six of our seven cases In the seventh case a large intragastric leiomyosarcoma the size of a grapefruit and attached by a moderate-sized base was removed by Dr Samuel F Marshall

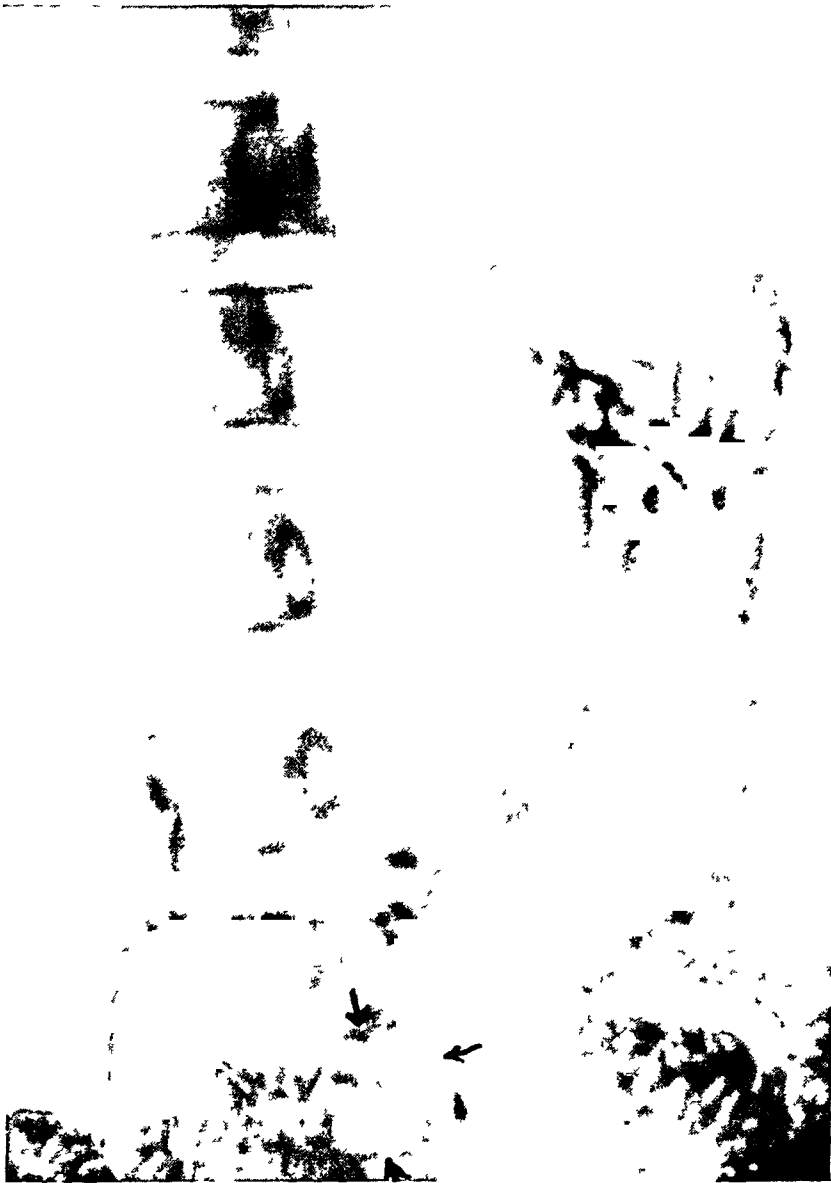


FIG 20—Case 7 Roentgenogram of the stomach showing tumor of the antrum

intragastrically, together with the attached section of the stomach wall, and the remaining defect in the stomach wall closed, the patient making an excellent recovery This was done after Doctor Marshall and I had examined the stomach with the abdomen opened and arrived at the conclusion that because of the size of the tumor one would have to accept either intragastric removal together with the portion of the stomach wall to which it was attached or a total gastrectomy Since the tumor was completely encapsulated and movable on its base, and since we did not know whether or not it was

malignant, the conservative procedure of local intragastric removal was chosen

The type of malignant degeneration occurring in these tumors is usually of low grade and for that reason, even in the patients with the multiple leiomyosarcomatous lesions involving the entire stomach as shown in Figure 5 of Case 2, total gastrectomy is distinctly justifiable. This patient, whose photograph is shown in Figure 4, three and one-half years after total gastrectomy for a leiomyosarcoma involving the entire stomach (Fig 6a), is able to eat nearly everything, to maintain her weight and, with the aid of

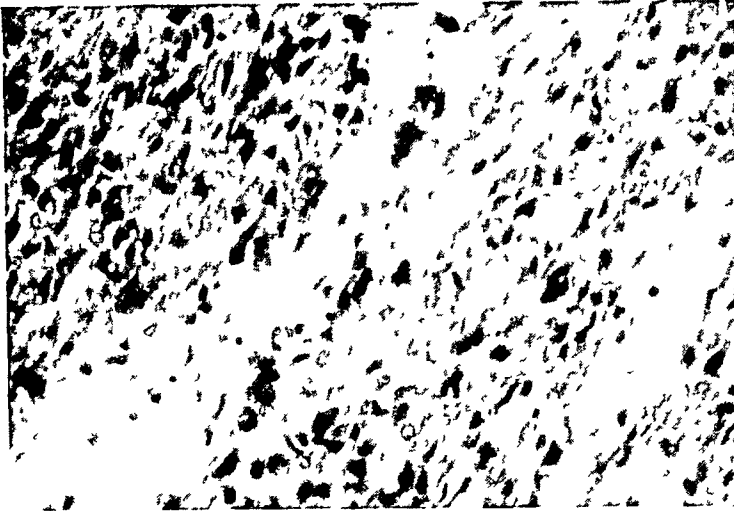


FIG 21—Case 7. Photomicrograph of portion of leiomyosarcoma showing marked edema of stroma, separating strands of atypical smooth muscle cells ($\times 300$)

liver, hydrochloric acid and iron, to maintain her hemoglobin and red count at a normal level. In an experience with complete gastrectomy, now amounting to 27 cases, there have been but seven deaths. Sixteen consecutive total gastrectomies have now been performed with but three deaths. It has, therefore, been demonstrated that the operation has been developed technically to a point where its mortality rate, when one considers the magnitude of the procedure, is justifiable. It has been demonstrated that these patients with no stomachs, and a loop of jejunum serving as a substitute for one, can maintain themselves adequately as to health, activity, body weight and blood picture. Time and further experience will determine the position of this operation for advanced carcinoma of the stomach. Its applicability, however, in sarcoma involving the entire stomach seems at its best since there exists in these cases, particularly those of the leiomyosarcomatous type, even a possible prospect of cure in some of the cases showing low grades of malignancy.

CONCLUSIONS

- (1) Gastric leiomyomata are by no means uncommon
- (2) They are frequently associated with hemorrhage, occasionally with pyloric obstruction and, not infrequently, sarcomatous degeneration

In any patient with hematemesis or melena the possibility of this lesion should be kept in mind. Because of the possibility of sarcomatous degeneration, the tumor should be removed by wide subtotal gastrectomy and even in the advanced lesions, involving the entire stomach, total gastrectomy may still be applicable and justifiable.

REFERENCES

- ¹ Boyd, William. Surgical Pathology. Pp 886. Philadelphia, W B Saunders Company, 1938
- ² Chaffin, L. Smooth Muscle Tumors of the Stomach. West Jour Surg, **46**, 513-524, October, 1938
- ³ Collins, F K, and Collins, D C. Surgical Significance of Gastric Leiomyomas. West Jour Surg, **46**, 188-194, April, 1938
- ⁴ Elason, E L, and Wright, V W M. Benign Tumors of the Stomach. Surg, Gynec and Obstet, **41**, 461-472, October, 1925
- ⁵ Matas, R. Pediculated Polypoid Fibroadenoma of the Stomach of the Ball-Valve Type, Causing Unusual and Complex Syndrome. Surg, Gynec and Obstet, **37**, 723-731, December, 1923
- ⁶ Minnes, J F, and Geschickter, C F. Benign Tumors of the Stomach. Am Jour Cancer, **28**, 136-149, September, 1936
- ⁷ Rigler, L G, and Ericksen, L G. Benign Tumors of the Stomach. Radiology, **26**, 6-15, January, 1936
- ⁸ Romanis, W H C, and Mitchiner, P H. The Science and Practice of Surgery. Pp 893. London, Churchill, 1937
- ⁹ Swain, B R, and Cooper, T V. Leiomyoma of the Stomach. Lancet, **1**, 428-429, February 19, 1938

CONGENITAL PYLORIC STENOSIS[~]

DAVID E. ROBERTSON, M.D.

TORONTO, CANADA

THE CAUSE of congenital pyloric stenosis is not known, although there are several theories. Fraser¹ subscribes to Thomson's² theory of the tumor being due to overaction of the stomach musculature and hence hypertrophy of the pylorus. Hurst³ says "It is clear that the obstruction is due to something which produces a much more powerful resistance than the simple absence of relaxation (achalasia). The only explanation is spasm." He believes "it possible that the tendency to spasm of the pylorus is the expression in an extremely exaggerated form of the constitutional condition called hyperthemic gastric diathesis, which manifests itself by hypertonus, hyperperistalsis and hyperchlorhydria, and occurs much more commonly in men than in women. The diathesis is often present in several members of a family—this would explain the rare instances in which two and even three or four members of the same family have hypertrophic pyloric stenosis." As opposed to Hurst's theory of hyperthemic gastric diathesis and those theories which deal with the basis of its being in a hypertonic child, one has the subsequent history of the cases that are cured by operation. My knowledge of the after-results is only of those cured by operative measures, and the subsequent history of these cases is that of a normal individual. In no case that we have been able to trace in our series has there been any subsequent history of digestive disturbance that would suggest a disability such as duodenal or gastric ulcer, or other disease which may be associated with hypertonicity. Strachauer,⁴ and others, describe the lesion as having been found in a seven-month fetus and in a stillborn child. Cockayne⁵ believes the condition has a genetic basis though the way it is inherited is still uncertain and an environmental factor may be necessary for its production in addition to a genetic one. The early age at which a well-marked tumor has been found, clinically and at operation, eight days in a case of this series, weighs heavily in favor of the condition being present before and at the time of birth, and this would seem to point to the genetic influence. Added facts, such as more than one case in a family (in our series five siblings apart from twins), speak strongly for the genetic etiology.

It is a condition that is most frequently found in the first-born of a family. In this series 51.8 per cent were first-born. This agrees with statistics published by other authors, but it seems to be a high percentage and challenges a rational explanation. The percentage of first-born children in the total number of births is greater in urban communities, where families are small. Yet even in such centers first-borns predominate (Table I).

There is reason to believe that more males are conceived than females

* Read before the American Surgical Association, St. Louis, Mo., May 12, 3, 1940.

TABLE I
Cases of Pyloric Stenosis

Order of Birth	Cases of Pyloric Stenosis		Average Births, Toronto	
	Number	Per Cent	Number	Per Cent
1st	144	51.8	4,748	41.2
2nd	61	21.9	2,730	23.8
3rd	41	14.7	1,627	14.1
4th	16	5.8	916	8.0
5th and over	16	5.8	1,476	12.9
Total	278	100.0	11,497	100.0

since a study of early miscarriages shows the percentage of males very high until figures at the time of birth show a slight preponderance only of males. Males are, therefore, less robust than females and have a poorer chance of surviving.

Twins, or a sibling twin, may have the condition. Sheldon⁶ states that in 1,000 cases of congenital pyloric stenosis, 1-43.4 cases is a twin sibling, while the ordinary 1,000 birth-ratio is 1-80 births. In our series, one case in 36.3 cases is a twin, while the ordinary ratio for Canada is 1-83.4.⁷ Cockayne⁵ describes two pairs of twins who were first cousins, all four were proved to have congenital pyloric stenosis at operation. The occurrence of the condition in monozygotic or maternal twins is almost positive proof of a genetic factor being the producer of the condition. In the cases recorded,

TABLE II
SUMMARY OF 12 CASES OF TWINS WITH PYLORIC STENOSIS*Hospital for Sick Children, Toronto*

Year	Initials of Twins	Sex of Twins	Type of Twinning
1914-1915	R R	♂* ♀	Fraternal
1917-1918	R McG	♀* ♂	Fraternal
1925-1926	B M	♂* ♂	Doubtful
	(Twin died. Parents describe the twins as identical, December, 1939)		
	A G	♂* ♀	Fraternal
1927-1928	Harvey and Grant I	♂* ♂	Fraternal
	(Reexamined November, 1939)		
1930-1931	Ross and Donald McF	♂* ♂	Fraternal
	(Reexamined December, 1939)		
1933-1934	R W	♂* ♀	Fraternal
1935-1936	William and Harry L	♂* ♂	Fraternal
	(Reexamined December, 1939)		
1937-1938	P W	♂* ♀	Fraternal
1938-1939	Garry and Glen T	♂* ♂*	Identical
	(Examined 1938)		
	Robert and Richard G	♂* ♂*	Identical
	(Examined 1938)		
	Erla and Arla C	♀* ♀	Fraternal
	(Examined 1939)		

* The symbol * indicates the condition

CONGENITAL PYLORIC STENOSIS

there are many reports of pairs of twins each having the condition, but few have been studied sufficiently to prove the type of twinning present⁷ There seems to be a reasonable doubt that identical twins are not both affected when the condition is found in one In our series, there were 12 pairs of twins, two pairs being identical twins All four had a tumor, proved at operation In all fraternal twins, one sibling only was affected (Table II) Multiple births are known to produce a disturbance of growth, and this may prove to be an environmental factor influencing the hypertrophy of the pylorus

This series includes all cases of congenital pyloric stenosis reaching the Hospital for Sick Children There were 28 cases which had no operative treatment, some being diagnosed only at autopsy, and who had received treatment for some other condition Of those cases treated without operation, ten were discharged as improved and 18 died Of these cases dying, the cause of death is given as bronchopneumonia, otitis media and septicemia, marasmus and acute intoxication Of the cases submitted to operation, *viz*, 402, 52 died subsequently from intoxication, malnutrition, decomposition, otitis media

TABLE III
CASES BY YEARS

	No of Operations	Cured	Died	Not Operated Upon	Cured	Died
1914	2	2				
1915	1		1	1	1	
1916	3	2	1	3	3	
1917	7	5	2	2	1	1
1918	11	8	3	11	5	6
1919	9	8	1			
1920	6	4	2			
1921	15	10	5			
1922	15	12	3	1		1
1923	12	11	1	1		1
1924	27	22	5			
1925	14	12	2			
1926	31	24	7			
1927	15	10	5	1		1
1928	25	24	1	1		1
1929	30	28	2	1		1
1930	14	12	2	2		2
1931	20	19	1	1		1
1932	22	18	4	1		1
1933	14	14		1		1
1934	9	7	2	1		1
1935	19	19				
1936	10	10				
1937	12	12				
1938	23	21	2			
1939	36	36				
Totals	402	350	52	28	10	18

and general infection, and in a few cases, there was a peritonitis due directly to the opening of the duodenal mucous membrane (Table III and IV)

TABLE IV
CONGENITAL PYLORIC STENOSIS

Hospital for Sick Children, Toronto—430 Cases

Males 352—81.9% Females 78—18.1%
Place in family not known—13 Others as below

1st	2nd	3rd	4th	5th	6th	7th	8th	9th	10th
213	84	61	31	14	6	5	2	1	1
51.1%	20.1	14.6	7.4	3.3	1.4	1.2	0.47	0.24	0.24

Treated by Operation	Died	Mortality
1914-1923 incl	81	19 24.4%
1924-1933	212	29 13.0%
1934-1939	109	4 3.6%
1914-1939	402	52 12.9%
Not operated upon	28	18 64.3%

The symptoms of pyloric stenosis are occasionally found within a few hours after birth. Vomiting has been known to have occurred as early as this and to have continued through until the condition was cured. Of the symptoms that are present in the disease, vomiting will be found to be one of the most outstanding. It is of a special character. Inasmuch as it is the result of a pyloric obstruction, it will be large in quantity and be free of bile discoloration. Loss of weight, which occurs in the normal infant for two or three days after its birth, will be found to continue on until, at three weeks, the infant may be less in weight than at the time of its birth. In spite of the vomiting and the loss of weight, the patient will be found to have a splendid appetite. It takes its nourishment with avidity. The stool is found to be bile-stained, but may be small and scanty and bearing some relation to the amount of food that gets through the pylorus. The infant is dehydrated, its skin is shrunken, and it has very little subcutaneous fat. It is fretful and cries a great deal. Examination of the abdomen shows the abdomen scaphoid with visible peristalsis to be seen to sweep from left to right, gaining in size and activity with the increased amount of food taken into the stomach. When a fastigium has been reached an explosive vomiting occurs which partially empties the stomach. The vomiting is characteristic in that the propulsion is such as to throw the vomitus a considerable distance from the lips of the infant. A stream may be shot out as far as 18 inches. It comes out through the nasopharynx and nostrils. On palpation of the abdomen, it is possible to feel an enlargement in the pyloric region. The tumor is to be felt by examination of the hypergastric region on the right side. Digital examination, just below the level of the costal margin and just lateral to the edge of the rectus, may palpate a hard nodule about the size of a large hickory nut. This nodule is movable and is more easily felt when

the peristaltic wave in the stomach has lifted up the pyloric nodule to a position where it is more superficial

Blood and urinary tests have no characteristic changes of diagnostic value

The diagnosis of this condition should be relatively simple. The history of loss of weight, vomiting, visible peristalsis, in an infant, is to be considered as a probable case of pyloric stenosis. The earliest case that has been operated upon by the writer was one eight days of age. It was found to have a well-marked and definite tumor. The symptoms may not appear until two or three weeks after birth and then a history is given of a sudden onset. At operation, a well-marked tumor may be found, which makes it difficult to explain why there should have been no obvious symptoms before the sudden onset.

In the diagnosis of a case of pyloric stenosis the examiner should, in suspected cases, have the patient stripped of all clothing, lying on its back, with a good light on the abdomen. The infant should be given some sweet water or glucose solution in a nursing bottle, and, as it nurses, the upper part of the abdomen should be observed. As the patient fills his stomach the epigastric region will be seen to fill out, and, presently, waves of peristalsis will be observed to originate in the left side of the abdomen and sweep across to the right. With an increasing volume entering the stomach the waves will be seen to increase in magnitude and speed. When they become very pronounced the patient is seen to stop nursing, draw its legs up and cry, and eventually when the waves have become of great magnitude, explosive vomiting occurs. The stomach being emptied of the larger part of its contents, the child will immediately again take the bottle in an endeavor to get some nourishment. It is an opportune time to palpate the right hypocostal region to examine for the presence of the pyloric tumor. The left hand lifting in the right flank of the patient assists the second finger of the right hand to identify the tumor in the epigastrium. An examination which has demonstrated visible peristalsis with projectile vomiting and the identification by palpation of a pyloric tumor may be considered as sufficient for diagnosis of an obstructive congenital pyloric lesion. A thin barium mixture may be given in order to obtain roentgenographic verification, but this type of examination is not to be encouraged as there is a certain danger associated with the giving of barium to an infant who has pyloric stenosis. The liability of the barium producing an acute obstruction in the very narrow lumen of the pylorus is a real danger. A proper physical examination of the infant will give all the needed information to enable one to make an accurate diagnosis.

The condition is best treated by operation. It has been claimed that the condition is amenable to well-supervised medical treatment. Yet such treatment, when successful is prolonged and difficult demanding the utmost in the parents' devotion in the care of a crying infant over many months. Whereas operative interference relieves the obstruction of the pylorus im-

mediately, and one may expect the function of the stomach to be immediately restored in large part or completely. This condition lends itself perfectly to surgical interference. It is surgery's best operative procedure. Any infant who has pyloric stenosis should be operated upon for the relief of the obstruction.

Steps must be taken to make it a good operative risk. The most important factor in the treatment of the infant is an early recognition of the condition. Surgery undertaken before there has been serious interference with the patient's health gives the best results, as is well demonstrated by the reports of Barrington Ward.⁸ When the patient has been allowed to experience a starvation of sorts for weeks its general condition will be much affected. Dehydration will be present and it must be overcome by the administration, intravenously, of suitable fluids, such as normal saline, glucose 5 per cent, and blood. When acidosis is present whole blood transfusions are indicated. The infant can then be considered safe for operation. There are no contraindications for operation except the unfavorable condition of the infant, and this can generally be corrected by intravenous therapy in from 24 to 48 hours, to a degree that will permit the surgical procedure.

When operation is finally decided upon, the question of an anesthetic becomes of importance. In this series, almost all types of anesthetics have been tried. The experience of the writer is that ethyl chloride and ether, or ether without the ethyl chloride to initiate anesthesia, is much the best method. Local anesthesia has not proved satisfactory, as it is very difficult to restrain a struggling infant. Inasmuch as the operation is simple and can be performed in a very short period of time under favorable conditions, a general anesthetic is the best. It will be found most useful to have a small section of board about 24 inches long and six inches wide. This board is padded. The infant is laid upon this, with the legs bound to the board, somewhat in the manner of a papoose. This arrangement controls the infant, so that if it be not deeply anesthetized it cannot flex its thighs or move its legs. Before the anesthetic is begun a catheter should be introduced into the patient's stomach and the stomach contents withdrawn. The stomach having been emptied, the anesthetist may proceed with the administration of ether. Conforming to the size of the infant's face, a simple wire mask covered with ten thicknesses of gauze is used.

Operative Procedure—The skin is prepared by washing with soap and water, drying, and then applying 2½ per cent iodine in 70 per cent alcohol. Standing on the right of the patient, an incision is made parallel to the right costal margin and about one-half inch below it. The inner extremity of this incision should be lateral to the edge of the rectus, and the incision need not be longer than 2½ inches. The skin and deep fascia having been divided, the external oblique is split in the direction of its fibers, the internal oblique is then identified and split in the direction of its fibers. The transversalis fascia and peritoneum are generally closely applied and can be divided as

one When this incision has been properly made through its entirety, the liver will be found to be exposed and will be blocking any attempt on the part of the abdominal parietes to extrude through the wound A finger can then be passed around the edge of the liver and one can immediately identify the hard tumor of the pylorus A pair of ring forceps without rubber or a pair of sponge forceps are then used to grasp the stomach, and by delivering part of this the pyloric tumor is, usually, easily drawn through the wound It is sometimes found that the tumor is very large and the wound may have to be enlarged to permit the delivery of it outside the abdomen The left thumb and forefinger then grasp the duodenum at the lower extremity of the tumor and squeezing the fingers together presses the lower part of the tumor presenting in the duodenum toward the stomach The tumor will be found to have an avascular line on its superior border This superior border is concave, the whole tumor having the appearance of a large cashew nut A simple incision about half an inch long and just deep enough to allow the engaging of the closed tips of tendon scissors is all that is required The closed points of these tendon scissors engaged in the wound are spread The tumor will be found to split from end-to-end, and through its thickness, until the mucous membrane of the pylorus is seen appearing as a white and glistening structure in the bottom of the split When the tension is taken off the scissors in the split tumor this mucous membrane will be found to bulge into the split It is not necessary to divide every last strand of the tumor at its lower extremity, and it is courting danger to attempt it All pyloric tumors project into the duodenum, as a cervix into the vagina When one endeavors to split the extremity of the tumor at its duodenal end, he will almost invariably open the mucous membrane and have soiling of the wound from stomach content, in addition to hemorrhage coming from the torn membrane When this event occurs it becomes necessary to suture this small opening as it has been known to produce peritonitis, which has ended fatally The writer believes that the squeezing of the duodenal end of the tumor, in such a fashion that it is expressed towards the stomach, permits one, when the tumor is split with the scissors, to have it sufficiently divided for all practical purposes When the tumor has been split in the avascular region, it will be found there is no hemorrhage occurring that requires any attention The tumor is dropped back into the abdomen No steps are taken to cover the split in the tumor by grafts or fat or strips of muscle The lower edge of the liver slides back into position, and one can close the peritoneum and different muscle layers without interference of abdominal contents extruding through the wound The writer uses No 0 catgut to close the different layers, and No 000 chromic catgut in the skin The wound is dressed by applying a small gauze strip over bismuth-formic iodide powder This dressing is slightly larger than the wound Mastisol is applied, surrounding the wound, and a section of gauze bandage is placed over the dressing and pressed on to the drying mastisol and trimmed off, so that the

whole dressing is not more than two inches wide and three or four inches long

Following the operation a transfusion of whole blood is administered when it is felt dehydration or shock requires it

Postoperative Feeding—One-half ounce of breast milk four hours after operation. Feeding increases one drachm every four hours until a total of 3 oz q 4 h x 5 is given, unless the child vomits, in which case the amount of feeding remains the same without any increase at the end of the four-hour period. After the amount of the feeding has reached 3 oz q 4 h x 5, it is changed back to the feeding given previous to operation, or started on 2 per cent L A M, 4-5 oz, q 4 h x 5

We have found this treatment satisfactory and see no reason why we should change it. Recently, it has been suggested that no feeding be given for 24 hours following the operation. This is based on the observation that infants vomit during the first 24 hours when they have been fed, and that barium administered shortly after operation is not emptied promptly from the stomach. In spite of this suggestion we feel that the infant should be fed four hours after operation and that occasional vomiting should not interfere with the routine of feeding.

We have had the cooperation of the staff in pediatrics, in the care of these cases. The cases are admitted to their wards, and when operation is performed the pediatrician still directs the feeding and general care. Without this cooperation the problem would be very difficult for the surgeon.

REFERENCES

- ¹ Fraser, John. *Surg Child*, 2, 814, 1926
- ² Thomson, John. *Edinburgh Hosp Rep*, 4, 121, 1896
- ³ Hurst, A F. *Brit Med Jour*, 1, 149, 1925
- ⁴ Strachauer, A C. *Minnesota Med*, 6, 131, 1923
- ⁵ Cockayne E A. *Lancet*, 1, 898, 1934
- ⁶ Sheldon, W. *Lancet*, 234(2), 1048, 1938
- ⁷ Ford, Norma, Brown, Alan, and McCreary, J F. To be published
- ⁸ Ward, Barrington. *The Abdominal Surgery of Children*. Oxford Medical Publication

DISCUSSION—DR WILLIAM E LADD (Boston, Mass.) There is no question but that the advance in treatment of congenital pyloric stenosis in the last 25 years has been one of the most striking improvements in the whole surgical field. I find this a difficult paper to discuss because the treatment has become so well standardized, because there are few controversial points and because I can find little or nothing to disagree with in Doctor Robertson's paper.

RESULTS IN 765 CASES OF PYLORIC STENOSIS

Years (Inclusive)	Number of Cases	Deaths	Mortality Per Cent
1915-1922	125	15	10.4
1923-1928	150	11	7.0
1929-1931	151	3	2.0
1932-1935	162	8	4.9
1936-1939	177	1	0.56

During the early part of the period, after we had adopted the present operation of pyloromyotomy, I believe our high mortality was largely due to having poor risk patients and to an inadequate knowledge of how to combat dehydration. Both of these handicaps have been largely overcome. The pediatrician now realizes that this condition is a surgical problem and refers the patient earlier, and our knowledge of fluid balance has been greatly improved. However, in spite of this situation, complications still arise which sometimes prove fatal.

In the earlier series, reported in the literature, some fatalities were reported from hemorrhage from the cut pylorus. This can be avoided by selecting, for the incision, the bloodless area on the superior surface of the pyloric sphincter. Cutting through the mucous membrane at the duodenal end of the pylorus is an error which it is easy to make. I think every member of my staff, including myself, has made this mistake once—but only once, and in no instance has a peritonitis resulted. This error is serious only if it is not recognized—then a fatality will probably follow.

Disruption of the wound has taken place several times in our series and in one instance caused a fatal peritonitis.

The several factors involved in this failure of wound healing are probably subclinical scurvy, low protein and edema, and technic of making and closing the incision. During the last two years we have given all these patients vitamin C before and after operation to overcome the first factor. We have probably paid too little attention to the question of low serum protein. We have varied our technic of wound closure. The last type of closure employed has consisted in medial retraction of the rectus muscle and closure by layers with silk supplemented by stay sutures to, but not through the peritoneum. Doctor Robertson's suggestion of a gridiron incision under the costal border and outside the rectus muscles has many obvious advantages and I plan to adopt it at the next opportunity.

The suggestion recently raised by Faber and Davis, of San Francisco, that feeding be withheld for a period of 24 hours, or more, does not appeal to me as being sound. Our present feeding regimen which is similar to Doctor Robertson's has proved eminently satisfactory.

DR ALBERT O. SINGLETON (Galveston, Tex.) I wish to discuss one phase of the problem of pyloric stenosis which Doctor Robertson has so ably presented, and this has to do with the incision which is employed.

The accompanying illustration (Fig. 1) illustrates the type of incision we have found very advantageous. It is made quite far to the right, since the pylorus in infants will be found much further to the right of the midline than in adults. With the posterior sheath of the rectus split in a transverse direction, sufficient room is obtained. With the pylorus delivered into the wound, there is no room for the evisceration of the small intestine and omentum, which may happen in these infants with their tremendous intra-abdominal pressure. This is particularly noticeable under local anesthesia which we are in the habit of using. Also, postoperative disruption cannot occur. Doctor Robinson's suggestion of making the incision still further to the right, even outside of the rectus muscle, may be a very good one.

DR EDWARD J. DONOVAN (New York, N. Y.) I was very much interested in Doctor Robertson's paper on pyloric stenosis, since he has brought out a great many facts, particularly in regard to the twins, that I have not heard discussed in relation to pyloric stenosis before. We have had no identical twins in our series, and my experience with this condition consists

of about 425 cases that I have operated upon personally. Our cases have followed those of Doctor Robertson very closely. We have found that the condition occurs about five to seven times more often in boys than in girls, that is, there are between 14 and 18 girls in each 100 cases. All nationalities are represented, and in a city where there is a large colored population there are about two colored children in each 100 cases.

We do not know any more about the etiology than anyone else, but have felt, because we have had several cases in premature infants with pyloric tumors that were very easily palpable, that the tumor was congenital in origin, and an associated pylorospasm caused the onset of symptoms between the

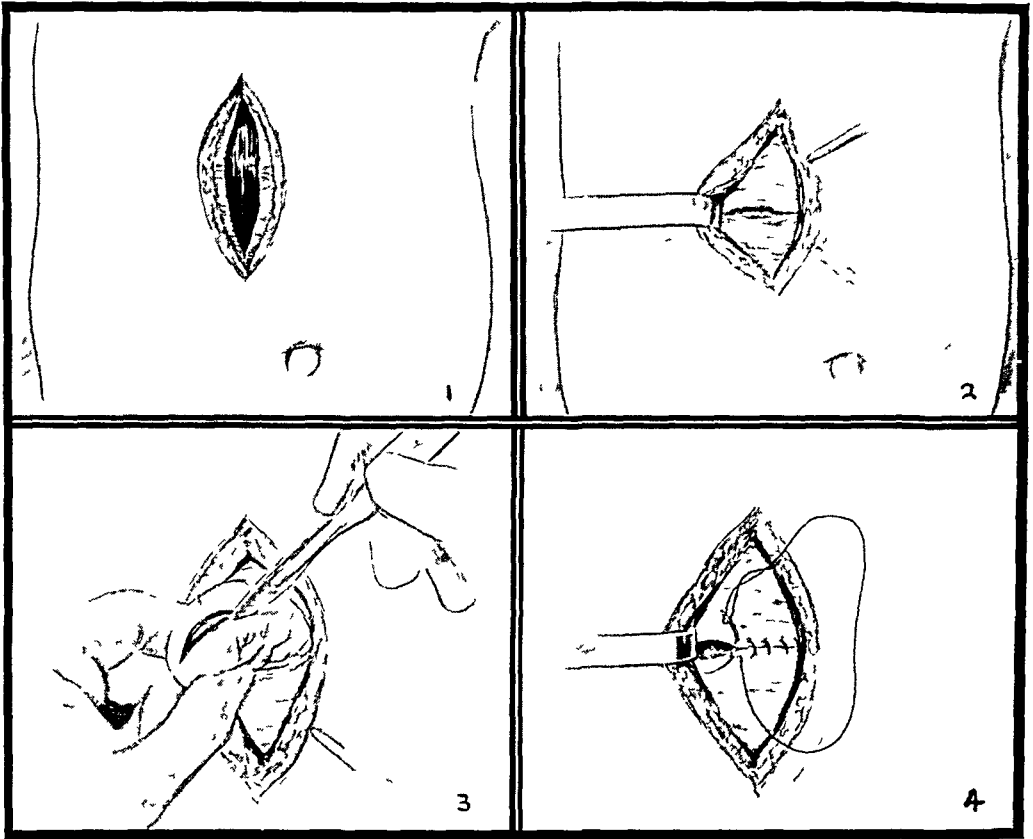


FIG 1—Drawings showing (1) the position of the incision employed, (2) the approach to and (3) the delivery of the pyloric hypertrophy, and (4) the method of closure of the wound

second and fifth weeks. We employ the Friedet-Rammstedt operation with a very high right rectus incision and retract the right lobe of the liver upwards in order to reach the pylorus. I think Doctor Robertson's incision may be better than the right rectus because we have occasionally found that it is difficult to deliver the pyloric tumor through this high right rectus incision. I will try some cases using Doctor Robertson's incision.

The operation that we perform is exactly the same as that done by Doctor Robertson except that we use a curved mosquito clamp to spread the muscle surfaces instead of scissors.

We believe in feeding these babies very promptly after operation. We give them 15 cc of water two hours after operation, and their first feeding, which consists of breast milk and barley water, three hours after operation.

Very few of these babies vomit after operation, if you empty the stomach completely in the operating room

We use ether in all cases and pass a stomach tube and completely empty the stomach before we make the abdominal incision

We have concentrated most of our attention on bringing the mortality down. When I started my series we were still operating upon them as emergencies. I remember very well going down to the Babies' Hospital one Sunday afternoon and operating upon one who had been sent in by a pediatrician, and the indication for operation in those days was that the baby was vomiting everything. No one seemed to give any thought as to whether the baby was able to stand such an operation or not. We have, in recent years, concentrated a great deal of our attention on the preoperative preparation, particularly the restoration of the fluid balance, and feel that the amount of vomiting is unimportant. Sometimes it takes between four and five days to prepare these babies for operation. In 1931, I reported my first 100 cases with one death and have had no deaths since then. In 1935, I reported 243 cases with the same one death. Last year, I reported 350 with the same death, and since that report I have had about 60 more and have lost none.

DR EDWIN M. MILLER (Chicago, Ill.) I hesitate to discuss a paper presented by one who has had a much wider experience than I in this field. During the past 20-odd years my experience has been limited to about 40 Rammstedt operations. My object in discussing this paper is to say that I feel one seldom has an opportunity to grossly and microscopically examine the pylorus of an infant upon whom this operation has been performed some time previously. This opportunity has come to me recently in a case that I operated upon in September, 1939—an infant, at that time two months old, weighing less than birth weight, presenting a typical picture in all respects with a definitely palpable pyloric tumor.

Last month this infant died of some cerebral disturbance, and they found in the records that I had operated upon the baby six months previously. They were kind enough, therefore, to turn the specimen over to me for examination.

I made a photograph, which was not a very good one, showing the duodenal mucosa and the anterior surface of the pylorus. I was surprised to find, on pathologic examination, how smooth this area was and the very little scar in this region. Transverse sections were made through the central portion of the pylorus, and the gross appearance across the center of the pylorus, apparently, differs somewhat, I would say, from the conception as illustrated in one of Doctor Robertson's photographs. Microscopically, it is difficult to decide where the incision had been made, that is, it was difficult for our pathologist to decide. He could not positively say, after thoroughly looking at this section a few days ago, where the incision had been made, but because of the thinner area in one quadrant I imagine that is the point where the operation had been performed.

DR WARREN H. COLE (Chicago, Ill.) Apparently we all agree that one of the most important features in bringing the mortality rate down in this disease lies in the fact that we are paying more attention to the electrolytic and fluid balance and bringing them up to normal before submitting these patients to operation. As some of the discussers have already mentioned, it is important to evacuate the stomach before the child is sent to the operating room. This will help the anesthesia and, certainly, will lead to a

smoother postoperative course, it may be necessary to evacuate the stomach again at the end of the operation if the child has swallowed a great deal of air.

It is likewise agreed that either general or local anesthesia may be used. I prefer local, and if, preoperatively, a mild sedative, such as second or nembutal is given, the local anesthetic will behave much better. I have never seen any ill effects from mild sedation of this style.

A second very important feature in the progress of the child postoperatively lies in the question as to how well the feedings are retained. I am quite convinced we can control this phase of convalescence to a large extent by watching the amount of feedings. I heartily agree that we should start feeding these children a few hours after operation, and should increase the amount rapidly up to about a normal feeding. However, if vomiting becomes significant during the course of the first few days, feedings should be reduced immediately to one-half the original amount, and increased gradually. In my experience this will almost invariably stop the vomiting. We will certainly grant that if over a given period of time a child took ten ounces of food and vomited eight, the situation would be much worse than taking five and vomiting none.

I should like to heartily endorse Doctor Ladd's statement about the use of vitamin C. I think this phase of therapy is tremendously important, and when you add closure of the wound with silk to that precaution, the incidence of wound disruption will be reduced practically to zero.

I wish to call attention to a final, and not insignificant point, namely, that a good spirit of cooperation with the pediatrician must be attained lest he attempt to treat these infants too long medically.

DR. WALTER ESTELL LEE (Philadelphia, Pa.) It would seem that nothing could be added to this discussion of the subject of congenital pyloric stenosis because everyone at the present time seems to be in agreement. I would like to express my personal appreciation of the suggestion of Doctor Robertson that a gridiron incision should be made in the subcostal region to the right of the semilunar line. I too have found, as Doctor Ladd has said, that the muscle-splitting incision is usually too far medially to be ideal.

May I suggest the addition of two procedures to the technic. For some ten years, we have operated entirely under local anesthesia. After the preliminary administration of luminal or nembutal, we give the child, shortly before operation, a sugar teat to suck. You may be surprised to hear that in the Quaker City the so-called sugar teat is made up of ten drops of paregoric and ten drops of whiskey or brandy to one ounce of a 5 per cent glucose solution. You will, likewise, be surprised how the babies take to this mixture, and also, more or less, amused by how promptly they become happily intoxicated.

The other suggestion has resulted from the observations of one of my assistants, Doctor Summey. In the past, one of our greatest difficulties, and most embarrassing complications, has been the failure to obtain primary union of the celiotomy wound in but a small proportion of cases. This involves merely the skin and the subcutaneous tissues, not the muscle sheaths, and we have not as yet had a wound disruption. After the removal of the skin sutures these infections promptly heal and we have had no herniae develop. Doctor Summey had been experimenting independently, and I was, eventually, informed by the nurse that they never had a breakdown in their wounds, as I did in mine! The explanation, apparently, is due to the fact that they have been using through-and-through unabsorbable mass sutures.

CONGENITAL PYLORIC STENOSIS

which pass through skin, subcutaneous tissues, muscle and peritoneum, and which are then tied over rolls of gauze after the skin edges have been approximated by interrupted mattress sutures of silk. Since employing this technic I have had primary union in every case. This, of course, is in line with Doctor Lahey's contention that in the closure of celiotomy wounds it is not necessary to employ layer sutures, and that through-and-through sutures of nonabsorbable material, down to the peritoneum, result in the lowest incidence of wound complications. It seems reasonable that the tissues in infants may not be capable of handling too much foreign body in the form of suture material.

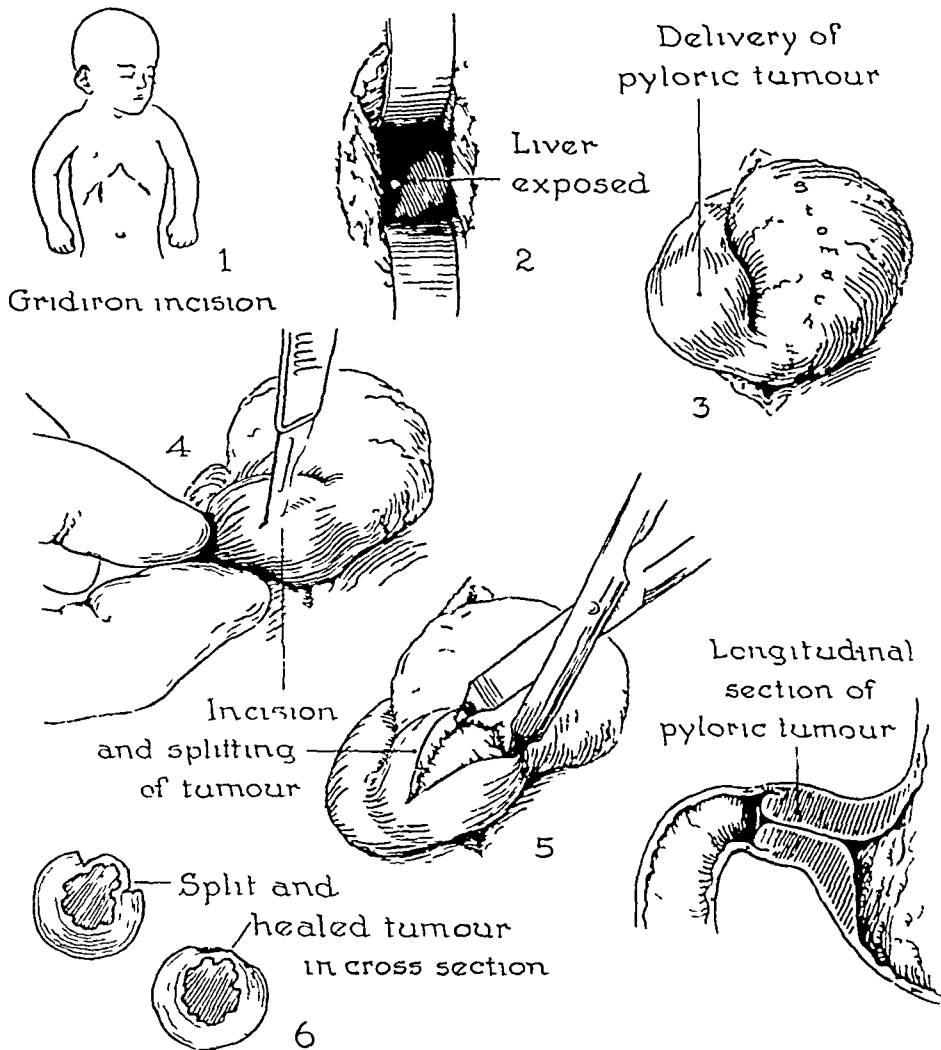


FIG. 1

DR D E ROBERTSON (Toronto, Canada, closing) It may be of interest to demonstrate by a drawing the gross specimen from a child who died of pneumonia three or four months after operation, which is a true representation of the condition present in the stomach (Fig. 1). In the pathologic specimen, just a thin layer of fibrous tissue covering the mucous membrane is to be seen. It is quite smooth externally and there is no muscle layer to be found.

In regard to the incision, I do believe that the best incision is the gridiron incision which can be closed by layers, and I think one should use No. 0 chromic catgut. I use No. 000 chromic catgut in the skin. Chromic catgut is used as I believe it is less irritating than plain catgut. When a sterile dressing is applied over the wound, with mastisol to hold it on, the wound need not be disturbed for ten days to two weeks.

ABDOMINAL NEOPLASMS OF NEUROGENIC ORIGIN*

HENRY K RANSOM, M D ,

AND

EARLE B KAY, M D

ANN ARBOR, MICH

FROM THE DEPARTMENT OF SURGERY, UNIVERSITY OF MICHIGAN ANN ARBOR MICH

THE NEUROGENIC TUMORS of the abdomen present many diversified and interesting features, both from the clinical and pathologic aspects. The purpose of this paper is a consideration of the clinical and pathologic features of 18 nerve sheath tumors and an attempt at their correlation. The neuroblastic tumors of the sympathetic and chromaffin systems were purposely excluded from this report (Table I)

TABLE I

ABDOMINAL NEOPLASMS OF NEUROGENIC ORIGIN

- I Nerve Sheath Tumors
 - A Benign
 - 1 Neurolemmoma (schwannoma—perineurial fibroblastoma)
 - 2 Neurofibroma (of type associated with von Recklinghausen's disease)
 - 3 Cirroid or plexiform neurofibroma
 - 4 Ganglionated neurofibroma
 - B Malignant
 - 1 Neurogenic sarcoma
- II Neuroblastic Tumors of Sympathetic System
 - 1 Sympathoblastoma
 - 2 Paraganglioma
 - 3 Ganglioneuroma

Embryology and Anatomy—To understand the histogenesis of the nerve sheath tumor, a brief review of the embryology and anatomy is essential. These tumors arise from the abdominal autonomic nervous system.

A peripheral nerve consists of an axis cylinder (neurite) which may or may not be invested by a medullary sheath (myelin) which is a product of the neurite. The next layer is the neurolemma, or what is commonly known as the sheath of Schwann. This is of neuro-ectodermal origin and is composed of a syncytium of Schwann cells. The third sheath is known as the sheath of Henle (or endoneurium) which is fibroblastic in character and consequently of mesodermal origin. This constitutes a single nerve fiber. Bundles of nerve fibers constitute fasciculi, and these are surrounded by a connective tissue layer known as the perineurium. About the entire nerve with its component fasciculi is a third connective tissue sheath, known as the epineurium.

The neurite arises from the medullary crests. The sheath of Schwann also has been shown, by ingenious and meticulous experiments by Harri-

* Read before the American Surgical Association, St. Louis, Mo., May 2, 1940

son,^{1, 2} to be neuro-ectodermal in character and to be derived from the ganglionic crests

Virchow, in 1863, divided the tumors of the peripheral nerves into two groups, the false neuromas and the true neuromas. The true neuromas were those composed of nerve fibers or nerve cells, while the false neuromas arose from the nerve sheaths. According to the present day conception, the only true neuromas are those arising from the primordial cells of the sympathetic and chromaffin systems and are neuroblastic in character, while the false neuromas are composed of a combination of sheath cells (Schwann cells) and a varying degree of fibroblastic tissue.

In reviewing the literature, one will find that there is no uniformity of opinion as to the histogenesis of nerve sheath tumors. Verocay,³ Masson,⁴ and Antoni⁵ feel that these tumors arise from the sheath of Schwann, and thus are of neuro-ectodermal origin. Mallory⁶ and Penfield^{7, 8, 9} believe that they arise from the connective tissue sheath of Henle, and thus are of mesodermal origin. Other observers believe, as we do, that in the present state of our knowledge, one cannot state with certainty the exact site of origin, for both types of tissue are said to form similar intercellular substances and to have the same histologic architecture. Special staining methods are still not specific enough to differentiate between these tissues to decide this problem. We do feel, however, that certain of the nerve sheath tumors, which we have designated "neurolemmomas," are composed primarily of Schwann cells, while there are others, such as the neurofibromas, that are composed of both Schwann cells and fibrous tissue. These latter tumors are usually found associated with a generalized neurofibromatosis (von Recklinghausen's disease). The neurogenic tumors of the abdomen are usually solitary and not associated with either multiple abdominal or cutaneous tumors. However, as Stout^{10, 11} comments unless one is particularly interested in this problem, the stigmata of von Recklinghausen's disease are often overlooked. In only two of our 18 cases was there evidence of such a constitutional disorder.

The benign nerve sheath tumors are of four types: (1) The neurolemmomas (schwannomas, or perineurial fibroblastomas), (2) the circoid or plexiform neurofibromas, (3) the neurofibromas of the type associated with a generalized neurofibromatosis, and (4) the ganglionated neurofibromas.

The *criteria* for the diagnosis of the neurogenic tumors were based upon the presence of specific histopathologic features characteristic of these tumors as demonstrated by special staining methods. Each neoplasm was thoroughly studied by special differential stains known to be of the utmost value in differentiating these tumors from other neoplastic lesions within the abdomen. The stains used were hematoxylin and eosin, Masson's trichrome, Mallory's phosphotungstic acid hematoxylin, and Perdrau's method for silver impregnation of reticulin. In Masson's trichrome stain, the Schwann cells stain pink and have pink protoplasmic end processes which anastomose with similar

end processes of the neighboring cells to form a syncytium. These end processes are encased in a sheath of greenish-blue staining collagenous-like material. The large wavy collagen fibers stain a deeper greenish-blue. Mallory's phosphotungstic acid hematoxylin stain stains the Schwann cell a pinkish-brown and the nucleus blue. The reticulin about the cells appears a yellowish-brown and the larger wavy collagen fibers are orange-brown. Perdrau's method of silver impregnation stains the reticulin black and gray-black while the collagen fibers appear violaceous.

Neurolemmomas—The abdominal neurolemmomas are confined largely to the stomach and retroperitoneal regions. While they are rare in the abdomen, they have been reported more frequently in the thorax, neck, trunk, and extremities. Furthermore, they are not necessarily solitary neoplasms for they may be associated with von Recklinghausen's disease. These tumors were



FIG. 1.—Case 3. L. P. Actual size section of a gastric neurogenic sarcoma (Fig. 11 A) showing its origin in the submucosa, the deep penetrating ulcer, and the whorled cut surface.

first described by Verocay, in 1910, and called by him neurinomas. In the gastro-intestinal tract, they arise from the sheaths of the sympathetic fibers of the submucosal and myenteric plexuses. They are reported as having a predilection for the myenteric plexus of Auerbach, but of five gastric cases in which this could be determined, two can be definitely shown to arise in the submucosa as shown in Figure 1, and three in the subserosa. Of the three intestinal cases, two arose in the submucosa, and one in the intermyenteric region. Definite attachment to nerves, however, was impossible to demonstrate.

Gross Characteristics of Neurolemmomas—Neurolemmomas are usually well encapsulated, slowly expanding neoplasms. They may be either solid, or cystic—usually the former. In only one of our cases was there marked cystic formation, as will be described later. There may be numerous small areas of cystic degeneration of small caliber throughout the tumor which may give it a spongy consistency. These tumors are usually of moderately firm consistency, being less firm than a carcinoma or pure fibroma. The

contour is oval, or round, and frequently nodular. The cut surface often has a whorled appearance and ranges from a gray to a grayish-yellow or grayish-pink color with scattered hemorrhagic areas appearing red. The yellow

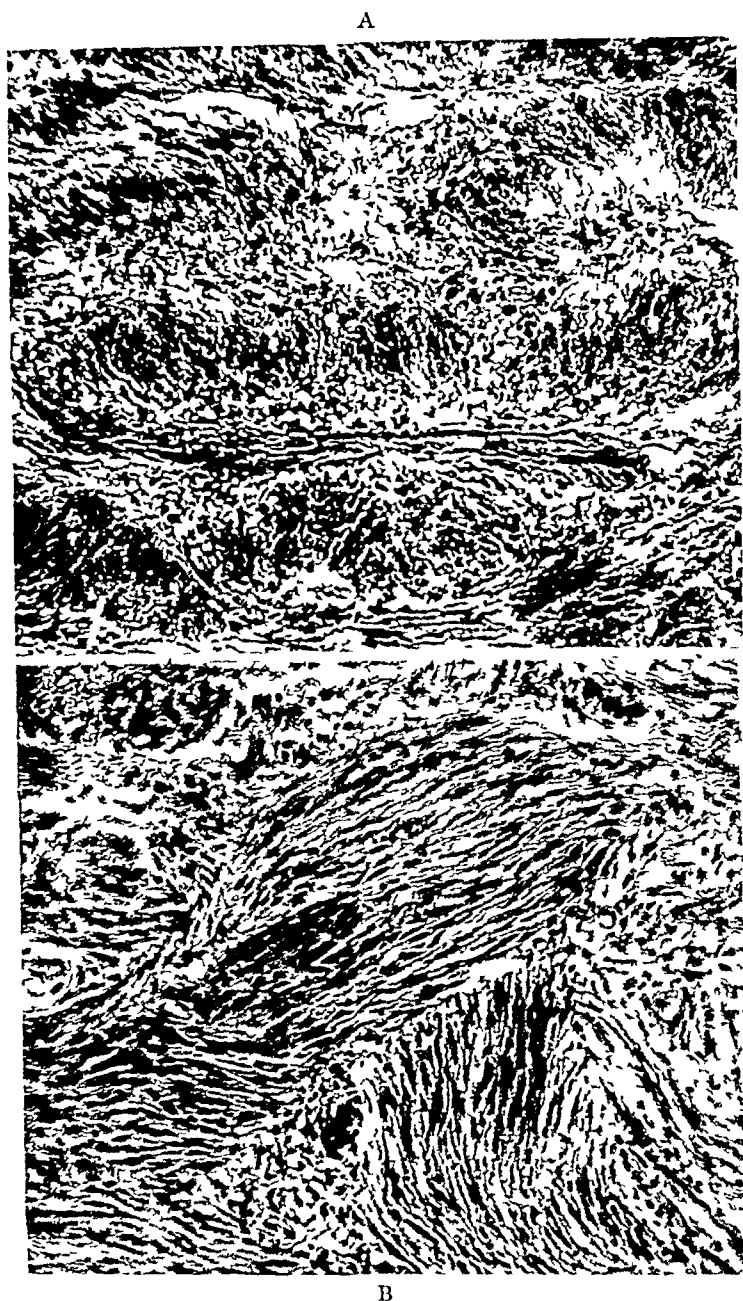


FIG 2 A—Case 2, R. B. Photomicrograph of a gastric neurolemmoma (Fig 10 A) showing marked palisade formation (Antoni Type A tissue) (H and E stain).

B—Case 8 G. K. Photomicrograph of a neurolemmoma of the gastrocolic ligament (Fig 14 A) showing interlacing bands, whorls, and palisade formation (Mallory's phosphotungstic acid hematoxylin stain).

areas are the result of necrosis. The tumors composed of Antoni's Type B reticular tissue are said (Geschickter¹²) to be larger in size when first recognized, gelatinous in consistency and to present a translucent gray-appearing cut surface. A characteristic gross feature of the gastric neurolemmomas is the deep-seated ulcerations of the mucous membrane surface.

Histopathology of Neurolemmomas—For the histopathology of neurolemmomas (Schwannomas, perineurial fibroblastomas) we are indebted to the painstaking researches of Masson, Verocay, Antoni, Mallory and Penfield. There are certain definite characteristics that identify them as neurolemmomas. Antoni states that they are composed of two types of tissue, which are known as Antoni Type A tissue and Antoni Type B tissue. Rarely is a neurolemmoma composed entirely of one type of tissue to the exclusion of the other. One type usually predominates, but both types may be found in varying quantities. The Type A tissue is orderly in character, consisting of palisaded rows (Fig 2 A) of slender elongated cells with blunt ends which give rise to long, thin, anastomosing protoplasmic end processes which anastomose with similar ramifications from neighboring cells to form a syncytium. These anastomosing end processes are covered by a thin layer of collagenous-like material. Throughout the tumor are seen large wavy collagen fibers. The nuclei are narrow, elongated, hyperchromatic and appear to be of an adult type. The important feature of this type is the palisade formation in which the cell nuclei lie parallel to each other. There is also a characteristic whorl formation of interlacing cords of cells (Fig 2 B) which differ from the whorls seen in fibromas. Masson accounts for the palisaded effect by Schwann cell proliferation in a longitudinal manner within the endoneurium. The palisading may not be found in all neurolemmomas. There may be present only whorling, interlacing bands and reticular type of tissue (Antoni Type B tissue). The tumors least likely to become malignant are those showing the most striking palisade arrangement.

Antoni's Type B reticular tissue is a loose meshed somewhat edematous or myxomatous appearing tissue without differentiation or orientation of the fibers (Fig 3). Antoni believed that there was a jellyfication and swelling of the collagenous fibrils and sheaths. This supposedly results in a separation of the tumor cells without interrupting their anastomoses to give a reticular architecture which takes the silver stain as shown in Figure 4. This belief is similar to that of Masson who contends that the reticular type of tissue results from degeneration.

Plexiform or Cusoid Neurofibromas—Plexiform neurofibromas appear to be a manifestation of a more constitutional disease. There were no examples of this type in our series. One of our patients who had neurofibromas of the jejunum also had an extensive plexiform neurofibromatous involvement of the pelvis, prostate, periprosthetic tissues, scrotum, left buttocks, and thigh. The plexiform neurofibromas result from an overgrowth of both the fibrous and schwannian elements of the nerve sheath within the perineurium, so that there is a large, tortuous, twisted, matted tumor mass attached to and often extending along the course of a nerve. This condition is known as elephantiasis nervorum. In none of these cases, even by the use of special stains, has it been possible to detect an actual proliferation of the nerve fiber (neurites) proper.¹³ Plexiform neurofibromas are seen in a

younger age group, frequently being present at birth. They are most commonly found about the head, face, and neck. Because of their proximity

FIG 3

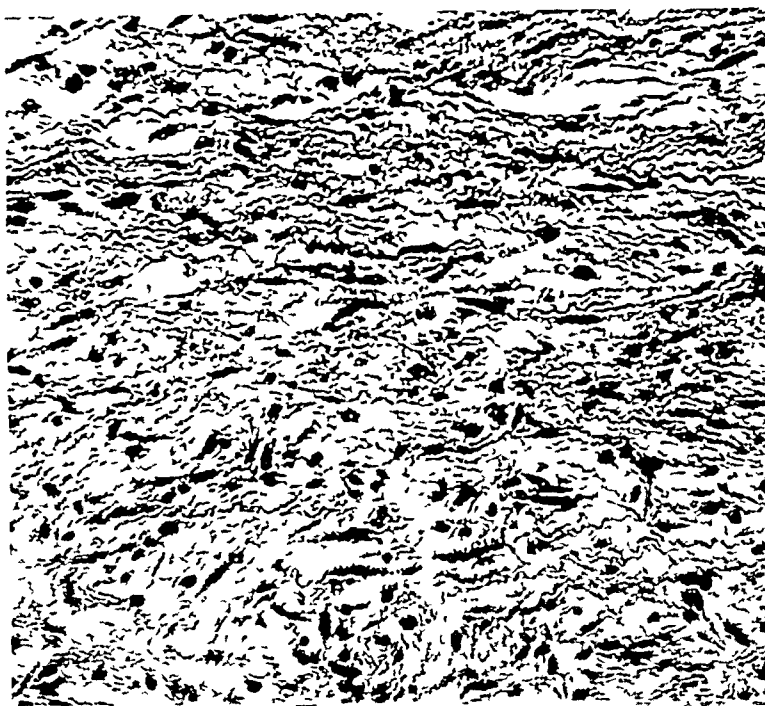


FIG 4

FIG 3—Case 11, J. S. Photomicrograph of a retroperitoneal neurolemmoma demonstrating the reticular type of architecture (Antoni Type B tissue). (Masson's trichrome stain)

FIG 4—Case 11, J. S. Photomicrograph, following Perdrau's method of silver impregnation, demonstrating the fine reticular architecture and the larger wavy collagen fibers of the microscopic section shown in Figure 3

to important structures, and the fact that they extend far along the nerve trunk within the perineurium, complete local excision is often impossible.

Neurofibromas—The term neurofibroma has been used by us to include

those nerve sheath tumors which are usually found associated with a hereditary generalized neurofibromatosis (von Recklinghausen's disease) In this condition, there is a congenital disturbance of the nerve sheaths resulting in multiple subcutaneous nodules, tumors of the deeper nerve trunks, and patchy pigmented areas These patients often have associated skeletal disturbances and mental deficiency The neurofibromas may, upon occasion, be isolated tumors

Structurally, the neurofibromas differ from neurolemmomas in that there are bands of elongated spindle cells occasionally arranged in whorls but which often have no characteristic arrangement They differ further in that there is a larger component of fibrous and fibroblastic tissue (Fig 5) There is little doubt that in the neurofibroma, there is a proliferation of both the cells of the sheath of Schwann, and those of the endoneurium and perineurium, while the neurolemmomas are composed primarily of Schwann cells Neurofibromas, likewise, may become malignant and give rise to spindle cell sarcomas The incidence of sarcomatous proliferation in neurofibromas associated with von Recklinghausen's disease has been quoted by Hosoi¹⁴ as being about 13 per cent

Ganglionated Neurofibromas—Ganglionated neurofibromas (Fig 6) may be either neurolemmomas or neurofibromas They are tumors arising from the sheaths about ganglia The ganglion cells are of an adult type and take no active part in the tumor growth They differ from ganglioneuromas, in that the latter are relatively differentiated neuroblastic tumors in which the tumor cell is the ganglion cell and commonly have associated with them the more immature cells of the sympathoblast and neuroblast The abdominal ganglionated neurofibromas are invariably retroperitoneal tumors They are slowly growing and well encapsulated Because of their location, they usually have obtained considerable size when first diagnosed and are consequently removed with difficulty

Neurogenic Sarcomas—As to the origin of neurogenic sarcomas, there are two possibilities One is that they arise upon neurolemmomas, the other is that they arise as sarcomas In support of the first view are the numerous cases reported in the literature in which incomplete excisions of neurolemmomas have resulted in malignant lesions later Also, in cases of neurogenic sarcomas examined for the first time, areas may be found in which the original architecture of the neurolemmoma is preserved (Fig 7 A and B) In support of the second view are those small incidental tumors removed at time of other operations, which histologically are shown to be sarcomatous The most convincing evidence favors the first view The criterion of the neurogenic origin of these sarcomas was based upon the presence in them of areas characteristic of neurolemmomas There were many other abdominal tumors that undoubtedly were neurogenic in origin but were not included because of the lack of demonstrable evidence

The neurogenic spindle cell sarcomas do not have the same prognostic significance as other types of malignancies Our experience closely simulates

that of others, that even though they are reported as malignant, in the majority of cases they fail to give rise to distant metastases but tend to remain locally malignant. Stout found that 74 per cent (48 of 65 cases) of peripheral nerve

FIG 5

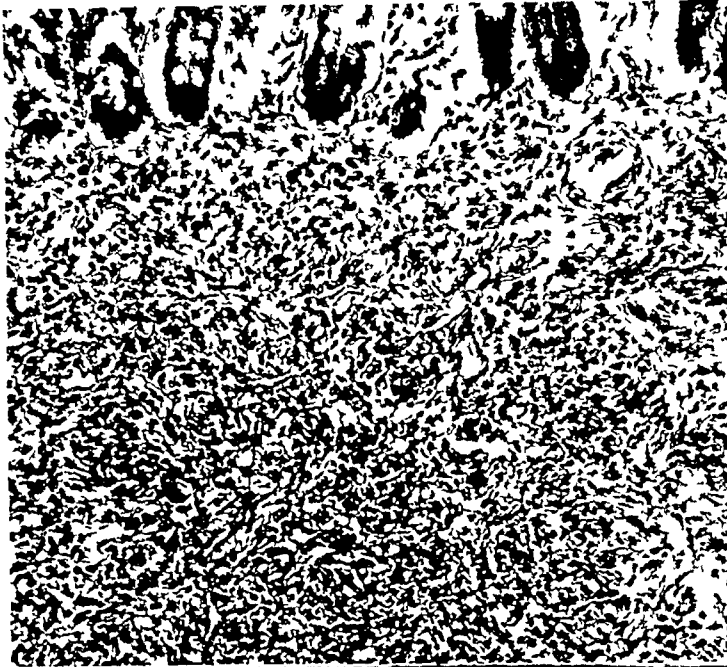


FIG 6

FIG 5—Case 7 D G Photomicrograph of an intestinal neurofibroma showing the irregular pattern of schwannoma and fibroblastic tissue

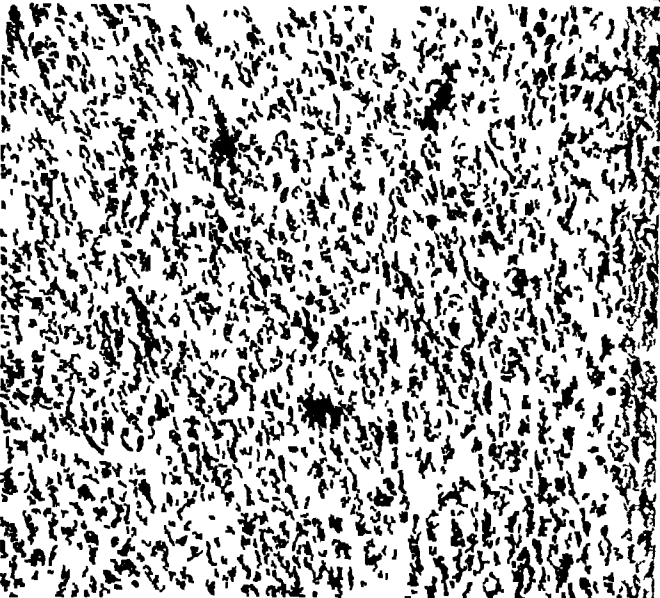
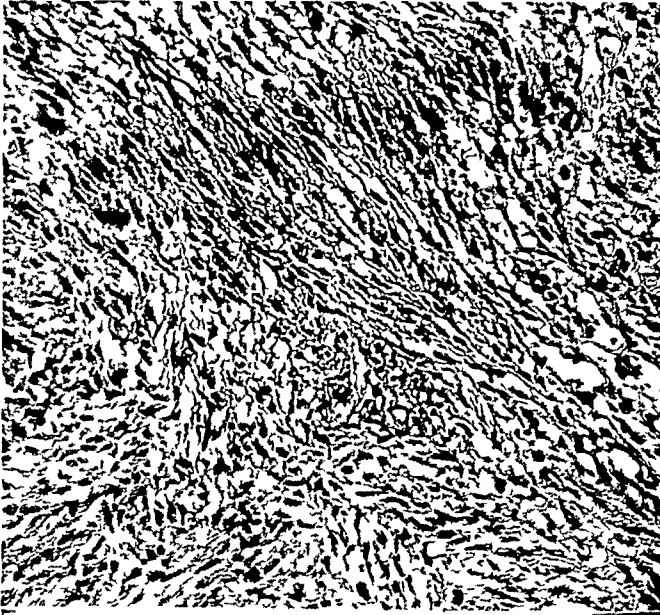
FIG 6—Case 12 J S Photomicrograph of a ganglionated neurofibroma showing the presence of mature ganglion cells

neurogenic tumors recurred following excision but in only 20 per cent (18 of 91 other similar cases) did they show evidence of metastases

Gross Characteristics of Neurogenic Sarcomas—Grossly, these neoplasms are of two types depending upon their location. The first are the large,

diffusely infiltrating neoplasms found in the retroperitoneal regions and mesenteries, and the second, the sarcomas found either in the gastro-intestinal tract, or incidental to other lesions for which the operation was performed

A



B

FIG 7 A—Case 3, L. P. Photomicrograph of the benign region of a gastric neurogenic sarcoma (Fig 11 A) which demonstrates the palisading and reticular type of tissue (Mallory's phosphotungstic acid hematoxylin stain)

B—Case 3, L. P. Photomicrograph of the sarcomatous region of the gastric neurogenic sarcoma (Figs 11 A and 7 A) demonstrating the loss of the original type of architecture

The first group is characterized by a large, nodular, solid (occasionally cystic), knotted mass that can be palpated diffusely infiltrating the adjacent organs, and often matting intestinal coils together. The cut surface usually shows

large, soft, necrotic areas appearing yellow, and other red hemorrhagic and cystic areas. The cystic areas contain a gelatinous substance. No evidence of encapsulation is noted. The second type, which are usually found arising in the gastro-intestinal tract, are often hour-glass or oval in shape, solid in consistency, and encapsulated except for an occasional break in the capsule where infiltration is seen. The sarcomatous proliferation may take place within the tumor and no evidence of an infiltrative border be present. This is especially true of the neoplasms arising upon the serosal surface.

Histopathology of Neurogenic Sarcomas—Histologically, the neurogenic sarcomas are composed of rather plump, hyperchromatic spindle cells with an occasional mitotic figure (Fig 7 B). The cells and nuclei may be of

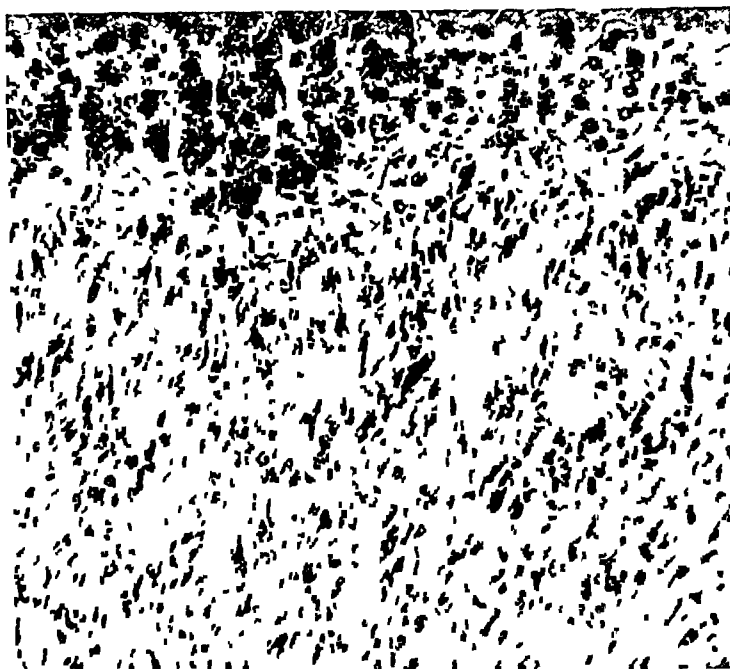


FIG 8—Case 9, D E. Photomicrograph of an hepatic metastasis of the mesenteric neurogenic sarcoma seen in Figure 15. Section demonstrates suggestive palisading even in the metastases (H and E stain).

various shapes and are less differentiated than those seen in the neurolemmoma. The cytoplasm is often scanty. The larger portion of the neoplasm has no characteristic architecture which would differentiate it from other spindle cell sarcomas. However there usually persist certain areas of whorling, interlacing bands of cells or palisades which identify its origin (Fig 7 A). For the most part, palisade formation is either scant, just suggestive (Fig 8), or entirely absent. The reticulin as well as the larger wavy collagen fibers are decreased in number and size. It has been reemphasized by Stout that the greater the number and thickness of the collagen fibers, the slower the growth will be, and the less likely the occurrence of metastasis.

General Clinical Features of Neurolemmomas, Neurofibromas and Neurogenic Sarcomas—Since the neoplasms under discussion arise from the investing sheaths of peripheral nerves, both somatic and sympathetic, it is possible,

theoretically at least, for them to occur in all parts of the body. Clinical observations, as evinced by the many cases recorded in the literature, show that the tumors have a predilection for certain sites such as the neck and the extremities, and that they are not uncommon in the thorax. Generally speaking, they are not frequently encountered among the structures of the abdominal cavity. With regard to their incidence in the various portions of the alimentary tract, again curious differences are noted. Thus, while certain organs such as the esophagus, colon and rectum seem to be singularly immune, in the stomach these tumors are relatively common. Unlike many of the more commonplace abdominal neoplasms, the neurogenic tumors are often discovered in unusual or even bizarre places such as the mesenteries, omenta or retroperitoneal spaces. Since they are expansively growing neoplasms, as their size increases, even in the case of the nonmalignant lesions, adjacent structures such as the stomach, intestine or colon may become secondarily involved in the neoplastic process. Such secondary involvement at times necessitates extensive or formidable operative procedures in order to eradicate the growth completely.

Even in the unmistakably malignant lesions (neurogenic sarcoma), distant metastases do not take place until relatively late in the disease. In only three of the eight neurogenic sarcomas in this series were distant metastases observed. Thus, since even the sarcomatous lesions tend to remain localized for a long period of time, prompt recognition of their presence and radical surgical removal will very frequently be followed by good end-results. Since the dividing line between the neurolemmoma and the neurogenic sarcoma is a somewhat arbitrary one, depending largely upon the degree of cellularity of the growth, and infiltrative tendencies, and since different areas of the same tumor may exhibit different histologic features, none of these tumors is to be regarded as entirely innocent, and prompt surgical removal of any such tumor is urgently demanded. It seems more than likely that a neurolemmoma may, at any time during its life history, assume malignant properties and become capable of giving rise to distant metastases. Study of the microscopic sections in several of our cases affords convincing evidence of this fact. This same point has been stressed by Harrington,¹⁵ who reports excellent results from surgical treatment in a comparatively large series of intrathoracic neurofibromas. He believes that early removal is clearly indicated since sarcomatous proliferation may take place at any time.

In our own personal experience the results from surgical treatment of the various forms of internal nerve sheath sarcoma have been more satisfactory than has been the case when dealing with similar lesions situated on the surface of the body and particularly with those arising from the large nerves or nerve trunks of the extremities. From a review of the literature, one gains the impression that others have had similar experience.

Neurogenic Tumors of the Stomach—Of the 18 neurogenic lesions comprising the series, six were neurolemmomas, three neurofibromas, eight neurogenic sarcomas, and one a ganglionated neurofibroma (Table II). Seven

NEUROGENIC TUMORS OF ABDOMEN

TABLE II

Neoplasm	No. of Cases
Neurolemmoma	6
Neurofibroma	3
Neurogenic sarcoma	8
Ganglionated neurofibroma	1
	—
Total	18

of these were located in the stomach, three in the intestines, two in the mesenteries, and six in the retroperitoneal space (Table III)

TABLE III

DISTRIBUTION

Location	No. of Cases
Stomach	7
Intestine	3
Mesenteries	2
Retroperitoneal space	6
	—
Total	18

Due to the confusion which exists in terminology, the meager data presented in many of the case reports and the differences of opinion among pathologists in the interpretation of their histopathology, it is difficult to estimate, with any degree of accuracy, the total number of cases of neurolemmoma and neurogenic sarcoma of the stomach which have been reported. In this connection, it is of interest to refer to certain of the more important communications of the various aspects of tumors of the stomach, which have appeared in the literature during recent years. Eusterman and Senty,¹⁶ in 1922, reported 27 cases of benign tumors of the stomach from the Mayo Clinic. They found the myomas and fibromas to constitute the largest groups, whereas no mention was made of tumors of neural origin. Eliason and Wright,¹⁷ in 1925, in a similar study, reported no instances of neurogenic tumors in their series of 50 cases. In their experience papillomas and polyps were the benign lesions most frequently encountered. In 1926, Balfour and Henderson¹⁸ presented the data in 58 cases of benign gastric neoplasms. While none of the tumors were classified as of nerve sheath origin, nevertheless 23 of the tumors were designated as fibromas, myomas, fibromyomas, adenomyomas and myxofibromas, a closely related group.

Arthur Purdy Stout (1935), in a very comprehensive discussion of the benign nerve sheath tumors, critically appraises the evidence submitted in the gastric tumors of neurogenic origin, previously reported. He accepts 32 cases as being truly nerve sheath tumors and to these adds three cases of his own. In a later communication concerned with the malignant tumors of the peripheral nerves, he included two additional cases, namely, those of Hartman and Shouldice.

Geschickter,¹⁹ in 1935, in his study of tumors of the digestive tract, found

among 962 malignant lesions, ten examples of nerve sheath sarcoma, three of which occurred in the stomach

Minnes and Geschickter²⁰ (1936), studying benign tumors of the stomach, mentioned 102 cases of neurofibroma among 931 cases of benign tumors reported in the literature. They concluded that neurofibromas of the stomach were not infrequent and calculated that such tumors constituted approximately 10.9 per cent of the recorded cases of benign gastric lesions. In their own series of 50 benign tumors from the Johns Hopkins Hospital, there was

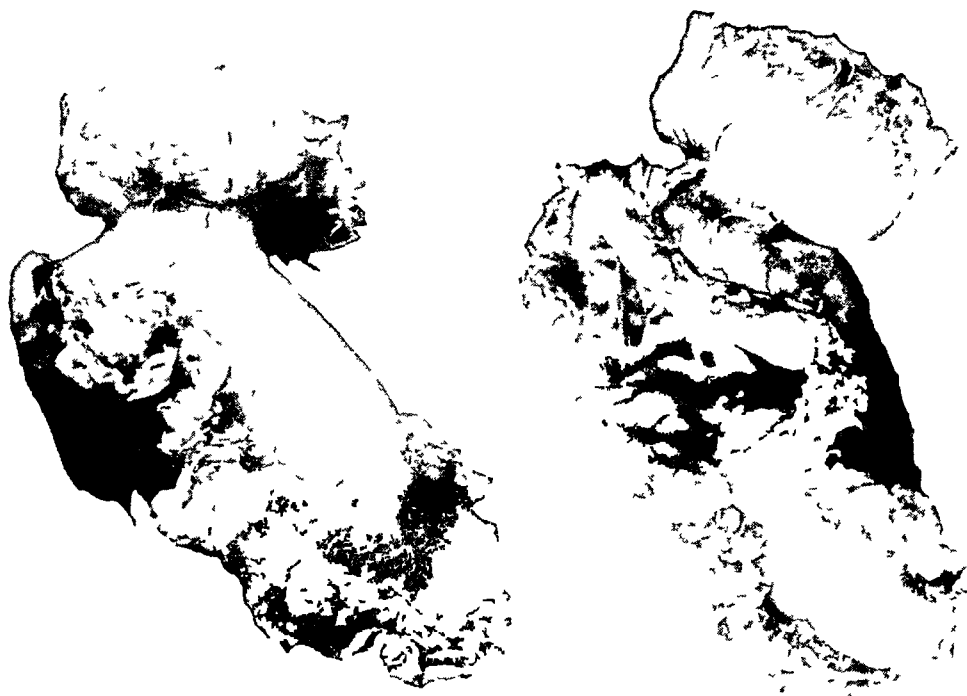


FIG. 9. A—Case 1. O. B. Photograph of an hourglass neurofibroma located upon the posterior wall near the greater curvature of the stomach.

one large neurofibroma accidentally discovered in a 78-year-old man who died of a ruptured bladder.

In two recent Cabot cases (No. 21112²¹ and 23312²²), the clinical records of patients with neurogenic sarcoma of the stomach are presented. In the former case, the patient, a man, age 46, gave a history of ulcer symptoms of long duration with repeated hemorrhages more recently. A spindle cell neurogenic fibrosarcoma was successfully removed at operation. The second case was that of a 64-year-old woman whose chief trouble was vomiting of blood over a five-year period. A neurogenic fibrosarcoma of the stomach was surgically removed.

In general these nerve sheath tumors are more apt to be encountered along the lesser curvature of the stomach and more often in the antrum or at the pyloric end of the viscus than in the cardia. There are conflicting statements in the literature regarding the frequency of involvement of the

anterior and the posterior gastric walls. On account of the greater ease of inspection and palpation of the anterior wall, it seems probable that more of the small incidental lesions have been recognized when in this location.

In the case of the benign lesions growth is usually slow, although, ultimately, such tumors may attain great size and become readily palpable through the abdominal wall. From its beginning in the gastric wall as growth proceeds the tumor may enlarge outwardly forming an extragastric, subserous

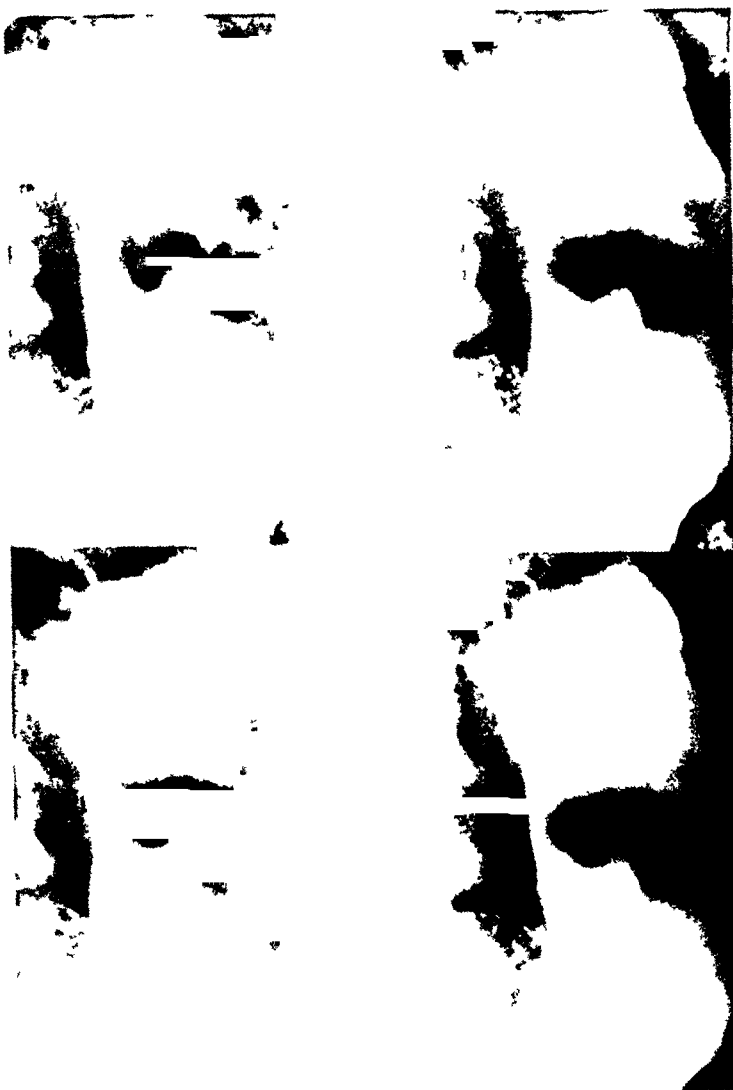


FIG 9 B—Case 1 O B Roentgenographic appearance of the neoplasm shown in Figure 9 A demonstrating the large polypoid rounded intragastric mass

or even pedunculated tumor. In other instances extension into the gastric cavity takes place resulting in an intragastric submucosal tumor. The mucous membrane becomes thinned-out and frequently shows ulceration over the summit of the tumor, an important point in explanation of the symptomatology and the roentgenographic findings of these tumors. An excellent demonstration of this was observed in Case 3. Growth in both directions results in a tumor of hour-glass or dumb-bell configuration (Figs 9 A and 10A).

Grossly, these neoplasms are gray, yellowish-gray, or pinkish-gray in color, often with a suggestion of translucency. The mass is ovoid or globular in

shape, and the surface is smooth, although there may be a variable degree of nodulation. On section, the tissue is found to be firm in texture and the

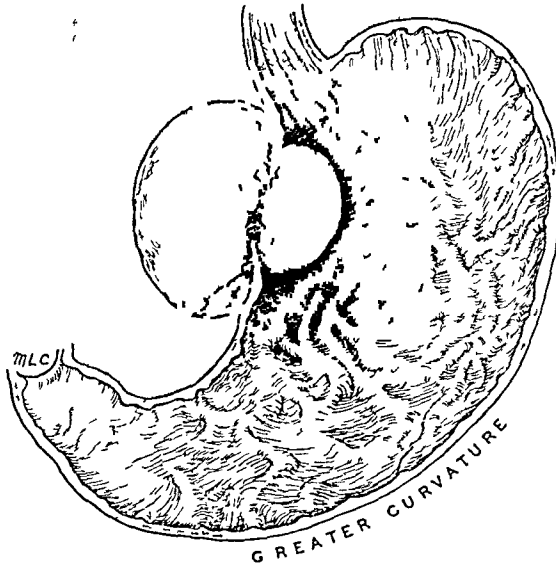


FIG 10 A—Case 2, R B Drawing illustrating the large hour glass neurolemmoma (Fig 2 A) located upon the lesser curvature near the cardiac end of the stomach



FIG 10 B—Case 2, R B Roentgenologic examination, June 8, 1938 demonstrates the appearance of the neoplasm shown in Figure 10 A with the ulcer crater at the superior aspect. Roentgenologic examination December 28, 1938, demonstrates the esophagojejunal anastomosis following the total gastrectomy.

growth is well circumscribed at its mural attachment. Occasionally, cystic degeneration may take place, resulting in a large solitary cyst or in some instances in a mass containing multiple smaller cystic cavities.

Not infrequently, smaller lesions are observed, being encountered quite by accident during the course of a celiotomy for some quite unrelated condition, *e g.*, gastric carcinoma, peptic ulcer, cholelithiasis, *etc.* In our group of seven neurogenic tumors of the stomach, three were of this type, two being removed at the time of partial gastrectomy for carcinoma, and one encountered and removed at the time of celiotomy for gallbladder disease. Of these three incidental tumors, the two associated with carcinoma were neurolemmomas while the third case proved to be a small neurogenic sarcoma.

Symptoms—While there are few if any symptoms which are pathognomonic of these tumors, there are a few complaints, or combinations of complaints, which are common to a fairly large number of the cases. By far the most important and the most suggestive symptom of which these patients complain is hematemesis. This is usually characterized by recurring massive hemorrhages often separated by long intervals of good health. Frequently in addition there are more or less typical ulcer symptoms, occasionally of long duration. Consequently an incorrect diagnosis of bleeding peptic ulcer is often made. The explanation of the bleeding is readily found in the ulceration of the gastric mucosa overlying the tumor (Fig 11 A). This point has often been stressed in the literature, and the gross finding of ulceration was very striking in several cases in the present series (Cases 2 and 3). Sometimes subjective symptoms may be entirely absent even after a tumor mass is detected. This is particularly apt to be true in the case of lesions with large extragastric extensions. Pyloric obstruction is occasionally noted although its occurrence is dependent largely upon the size and position of the tumor. Rarely a pedunculated intragastric lesion may prolapse through or into the pyloric ring, thereby causing obstructive symptoms. Obviously the small, accidentally discovered tumors produce no symptoms *per se*, or if they do, they are overshadowed by the symptoms relevant to the major disorder.

Examination—Usually, few significant findings are noted on physical examination, in fact, the remarkable feature is the good state of nutrition of the patient in spite of a long history of illness and of repeated hemorrhages. Infrequently an abdominal tumor mass may be felt. Laboratory investigations often reveal a secondary anemia and the presence of occult blood in the stools. The gastric analysis is of relatively little assistance in arriving at a correct diagnosis. By far the most important evidence is to be obtained from roentgenologic study. Especially in the case of lesions on the lesser curvature, the usual findings of benign gastric tumor are seen following the ingestion of the barium meal. Thus, there is apt to be a rounded mass, with a smooth contour projecting into the lumen of the stomach (Figs 9 B and 10 B). This appearance is exactly the same as that seen in the cases of leiomyoma, and as in the cases of leiomyoma and leiomyosarcoma, the barium often clearly marks the small central ulceration over the tumor responsible for the hemorrhages (Figs 10 B and 11 B).

Treatment—Wide surgical excision or resection is the treatment of choice

While local excision may suffice for some of the smaller lesions, in the case of the larger tumors, adequate removal is ordinarily possible only by partial

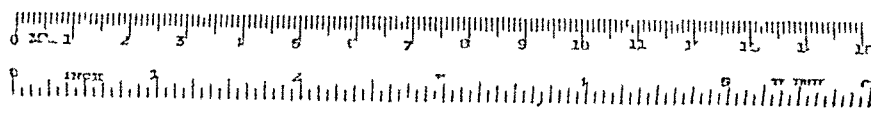


FIG 11 A—Case 3 L P Neurogenic sarcoma at the pyloric end of the stomach (Fig 7 A and B) demonstrating the large ulcer craters and its intramural location

or even total gastrectomy. While the neurolemmomas tend to recur locally following incomplete operations, if removal is adequate, the prognosis is

usually excellent. Even in the cases of neurogenic sarcoma, the prognosis is reasonably good, providing an adequate resection is performed. Since distant metastasis does not take place at an early date, and since involvement of the regional lymph nodes is not an important matter to be reckoned with, a thorough removal will often effect a cure. In the one case of neurogenic sarcoma, in which the entire specimen was available for study, detailed examination of the cleared specimen for lymph nodes showed no evidence of lymphogenous metastases—in contradistinction to the absence of metastases

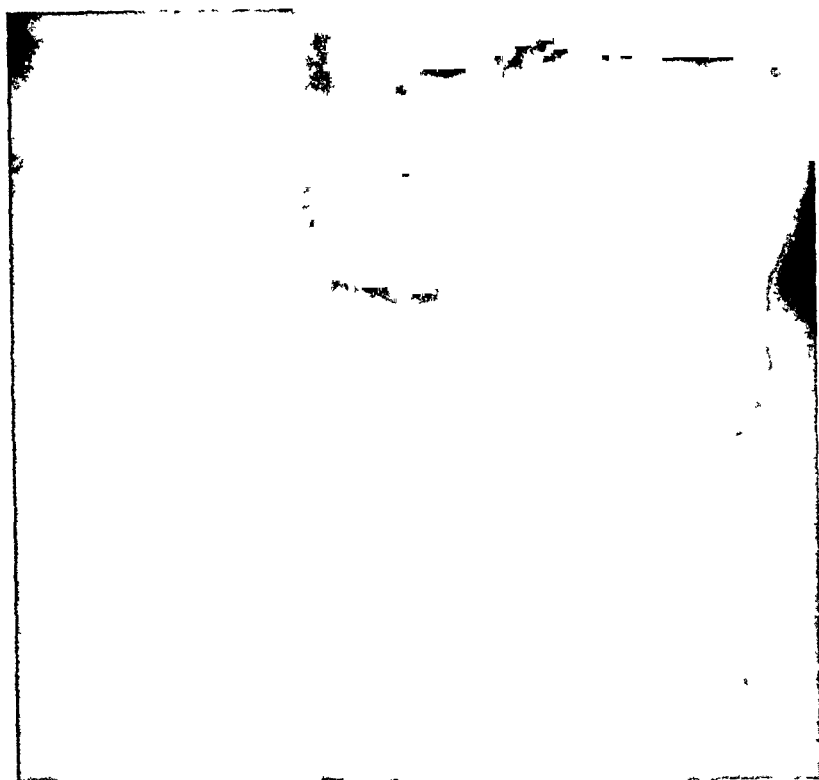


FIG. 11 B—Case 3, L. P. Roentgenographic appearance of the neoplasm seen in Figure 11 A demonstrating a large intragastric mass in the pyloric antrum and flecks of barium in the ulcer craters

in only four of 50 cases of carcinoma of the stomach studied in a similar manner. In fact, the prognosis is distinctly better than in the case of carcinoma of the stomach of the same magnitude.

Seven tumors of nerve sheath origin were situated in the stomach in our series, three of these being of sufficient cellularity to warrant a diagnosis of neurogenic sarcoma. The remaining four tumors were neurolemmomas (Table IV). All were isolated tumors, and none of the patients in this group showed any of the stigmata of von Recklinghausen's disease. In each of the four cases in which the neurogenic tumor was the primary and sole lesion, the chief complaint was that of massive hemorrhages. In two of these cases partial gastrectomy was performed, whereas in one, total gastrectomy was necessary due to the high position of an hour-glass tumor on the lesser curvature. In the remaining case, a very large tumor which arose from the posterior wall of the stomach filled the omental bursa and was firmly adherent to the posterior wall of the bursa over a large area. Removal was impossible,

TABLE IV

NEUROGENIC TUMORS OF STOMACH

Neurolemmoma	4
Primary lesion	2
Incidental	2
(Gastric Ca)	
Neurogenic sarcoma	3
Primary lesion	2
Incidental	1

Symptoms

Hemorrhage	4
None (tumor incidental)	3

and only a sufficient amount of tissue for biopsy was removed by means of the electrosurgical loop. Microscopic examination showed this to be a neurogenic sarcoma. There were no deaths in this group of gastric neoplasms. The following case abstracts illustrate the important clinical features of primary neurogenic tumors of the stomach.

ABSTRACTS OF CASE REPORTS ILLUSTRATING IMPORTANT CLINICAL FEATURES
OF PRIMARY NEUROGENIC TUMORS OF THE STOMACH

Case 1—O B, white, female, age 37, a Russian-Jewish housewife, was admitted to the hospital, April 30, 1936, with a complaint of gastric hemorrhages. She had been quite well until one month prior to admission, when she suddenly felt nauseated and vomited a large quantity of blood. Subsequently she passed several tarry stools. Two days later she experienced a second episode of bleeding. There was no antecedent history of abdominal pain or discomfort, and there had been no digestive symptoms. Since the onset of the trouble she had been on a strict ulcer dietary regimen. Roentgenologic studies elsewhere revealed a lesion in the stomach, thought to be a carcinoma.

There were no significant findings on physical examination. Laboratory studies showed the urine to be normal, the Kahn reaction of the blood to be negative and the leukocyte count to be 4,500, with a normal differential. The erythrocyte count was 2,800,000 and the hemoglobin content 52 per cent. The gastric analysis showed absence of free hydrochloric acid. The reaction of the stool to the benzidine test was negative. Roentgenologic examination disclosed a rounded, lobulated mass within the lumen of the stomach, situated just above the midpoint. It was considered to be a polypoid, primary gastric neoplasm (Fig 9B).

Because of a slight upper respiratory infection, she was discharged from the hospital, May 6, 1936, and returned for operation, May 11, 1936. A celiotomy was performed, May 14, 1936. The lesion in the stomach was located near the midpoint. It proved to be an hour-glass type of tumor, with a large intragastric projection and a larger extragastric portion of the tumor extending into the omental bursa. It was removed by means of a high gastric resection. Convalescence was uneventful except for a slight wound infection which responded promptly to treatment. She was discharged from the hospital, June 7, 1936. She returned for examination, July 7, 1936, feeling well and in excellent health. She was last heard from, April 23, 1940, at which time her general condition was excellent.

*Pathologic Examination**—Gross The specimen was a segment of stomach 11 cm

* The restudy of the gross and microscopic specimens of all cases reported, and the present interpretation of the latter, after subjecting them to newer staining methods, has been undertaken by Dr Earle B Kay.

long Near one end there was a large mass with a smooth surface This apparently arose within the wall of the stomach It appeared as two connected nodules One measured 6x5x3 cm and protruded into the lumen The other was subserous and measured 6x7x3.5 cm

Microscopic The neoplasm is composed of spindle cells having plump, oval nuclei arranged in interlacing bands and whorls An occasional area suggestive of palisading, but no true palisades are found A large portion of the neoplasm is reticular in character Perdrau's silver stain demonstrates a very fine reticulum Very few larger collagen fibers noted Masson's trichrome stain clearly demonstrates the histologic features of the Schwann cell with its pink protoplasmic anastomosing end processes which are encased in a thin sheath of greenish-blue collagen Mallory's phosphotungstic acid hematoxylin stain shows the Schwann cells with blue-staining nuclei, pink cytoplasm and the cytoplasmic end processes ensheathed in a layer of orange collagen *Pathologic Diagnosis* Neurolemmoma

Case 2—R. B., white, female, age 40, a Jewish housewife, was admitted to the hospital, June 7, 1938, complaining of attacks of vomiting blood The first episode occurred one year prior to entry, and at this time tarry stools were also noted for several days following the vomiting of a large quantity of blood A second attack occurred six months previously and a third one three weeks before admission Since the last attack she had noticed shortness of breath, palpitation, and ease of fatigue There had been no appreciable weight loss The physical examination disclosed no significant findings The urine was normal Gastric analysis (with histamine) showed the presence of free hydrochloric acid in normal amounts The reaction of the stool to the benzidine test was positive (four plus) Blood examination Leukocytes 6,700, with 56 per cent polymorphonuclear leukocytes, erythrocytes 4,430,000, hemoglobin 58 per cent The total plasma proteins were 4.9 mg per cent The albumin was 3.0 mg per cent and the globulin 1.9 mg per cent, with an A/G ratio of 1.6 The plasma chlorides were 574 mg per cent The Kahn reaction of the blood was negative Roentgenologic examination showed a gastric neoplasm involving the upper portion of the lesser curvature, and normal visualization of the gallbladder (Fig 10 B) A peritoneoscopic examination, made June 15, 1938, showed no evidence of metastatic carcinoma in the liver and no peritoneal implantation metastases

Accordingly, celiotomy was performed, June 20, 1938 High on the lesser curvature of the stomach was an hour-glass-shaped tumor, one portion of which projected into the cavity of the stomach and the other into the peritoneal cavity The upper portion of the tumor mass was only about 3 cm from the junction of the stomach with the esophagus Removal was accomplished by total gastrectomy Convalescence was uneventful and she was discharged from the hospital, July 14, 1938 At the time of her last visit to the Out-Patient Department, in November, 1939, her condition was found to be satisfactory, and check-up roentgenologic studies showed the esophagojejunal anastomosis to be functioning properly

Pathologic Examination—Gross (Fig 10 A) The specimen measured 19 cm along the greater curvature and 12 cm along the lesser curvature On the lesser curvature, and at the uppermost part of the specimen, was a tumor mass measuring 8x7x2.5 cm This was nodular and firm It appeared to arise in the wall and raised both the serosal and the mucosal surfaces involving them The mucosal surface was pitted but not grossly ulcerated There was no evidence of invasive spread

Microscopic (Fig 2 A) Large encapsulated, expansively growing neoplasm showing marked palisading of the nuclei with tendency to whorl formation The tumor is very vascular Many of the whorls are arranged about blood spaces The cells are spindle-shaped with round, plump nuclei A small amount of pink-staining cytoplasm with anastomosing end branches forming a syncytium is seen Perdrau's silver stain shows fine reticulum which is separated by large bands of collagen Masson's trichrome stain demonstrates again the pink-staining spindle cells giving rise to pink-staining syncytial fibrils Scat-

tered throughout the section are irregularly dispersed green and greenish-blue collagenous fibers Mallory's phosphotungstic acid hematoxylin stain demonstrates the spindle cells with their plump, blue nuclei and diffuse chromatin granules, and the larger collagen fibers are stained orange brown *Pathologic Diagnosis* Neurolemmoma

Case 3—L P, white, male, age 51, a merchant, was admitted to the hospital, February 13, 1940, complaining of dizziness, fainting spells and blood in the stools For one year previously he had noticed progressive weakness One month before entry, while at work, he suddenly fainted, and following this he passed a large tarry stool A few days later a similar episode occurred A roentgenologic examination, made elsewhere, resulted in a diagnosis of a bleeding gastric ulcer being made, and he was placed on an ulcer dietary regimen with amphogel One week prior to admission, check-up roentgenograms were taken, during which examination he fainted He had lost no weight, and gave no history of nausea or vomiting However, he had experienced slight epigastric pain following meals This had been relieved by food and soda

Physical examination disclosed no significant findings The urine was normal The leukocyte count was 4,000, the erythrocyte count 2,500,000, with a hemoglobin content of 30 per cent The guaiac test of the stool was positive Gastric analysis showed free hydrochloric acid in normal amounts The Kahn reaction of the blood was negative Roentgenologic studies showed an irregular filling defect in the distal third of the stomach (Fig 10 B) The appearance was that of a gastric carcinoma Following three blood transfusions, a celiotomy was performed, February 20, 1940 A large mass was found in the anterior wall of the stomach in the prepyloric region This appeared to be a benign tumor It was removed by partial gastrectomy The postoperative course was uneventful He was discharged from the hospital, March 11, 1940

Pathologic Examination—Gross (Fig 11 A) The specimen consisted of the lower portion of the stomach Upon the anterior wall there was a large intramural neoplasm measuring 8.6x3 cm, which extended down to the pylorus In the center of the neoplasm were three deep ulcers extending through the mucosa down to the neoplasm

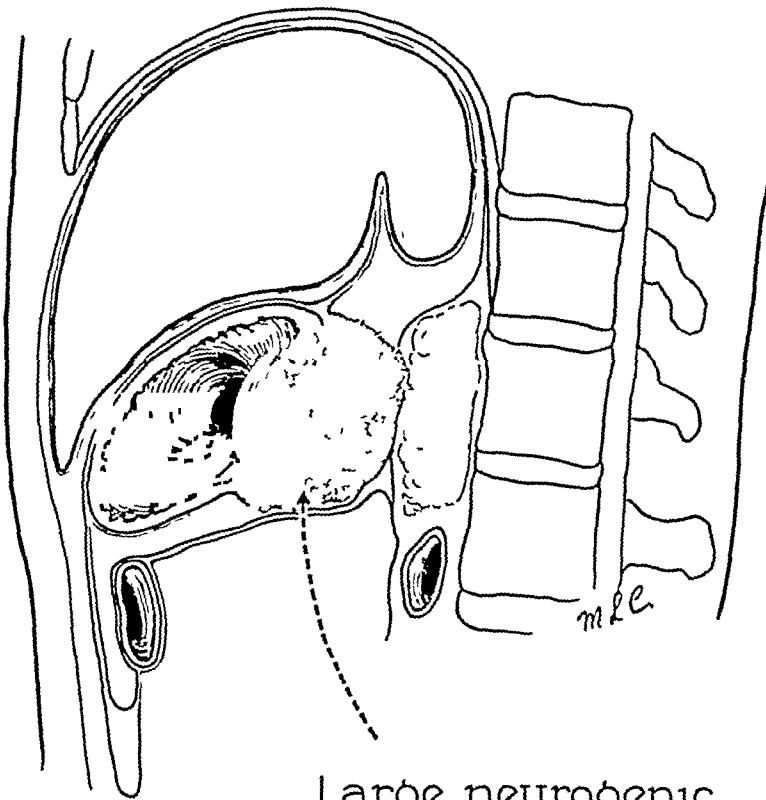
Microscopic (Fig 7 A and B) A cellular neoplasm showing areas of palisading, other areas show whorls and reticular architecture Masson's trichome and Mallory's phosphotungstic acid hematoxylin stains demonstrate the Schwann cells with their anastomosing protoplasmic ramifications Fine reticular net work seen between the cells A large portion of the neoplasm has undergone sarcomatous proliferation with loss of the original architecture Such regions show closely packed hyperchromatic spindle cells in no characteristic arrangement The mucous membrane overlying the neoplasm shows ulceration, the ulcer craters penetrating deeply into the underlying tissue *Pathologic Diagnosis* Cellular neurolemmoma with areas of neurogenic, spindle cell sarcoma

Case 4—J P, white, male, aged 35, an Austrian bricklayer, was admitted to the hospital, May 10, 1931, complaining of headaches, midepigastric pain, and vomiting of blood His health had always been excellent until two years previously, when he began to have pain following meals, the pain being relieved by food and soda Fourteen months previous to his admission he had had a severe gastric hemorrhage At this time, he had vomited a large amount of blood and had fainted He was treated elsewhere for three weeks Roentgenologic studies at that time showed evidence of a peptic ulcer He was placed upon an ulcer dietary regimen, with alkalis He adhered to this for nearly a year, during which time his health had remained fairly good Three weeks before admission he noticed that the stools were tarry and there was a recurrence of the epigastric pain Three days before his admission, he had another severe hemorrhage Following this he had been able to eat practically nothing and was so weak that he had to remain in bed nearly all of the time While he had gradually gained in weight during the past year, there had been a considerable weight loss during the past few weeks

Physical examination revealed marked pallor of the skin and mucous membranes In the epigastrium, just below the xiphoid, there was an area approximately 6 cm in diameter which was markedly tender to palpation No masses could be felt The urine was

normal The leukocyte count was 8,800, with 61 per cent polymorphonuclears, the erythrocyte count was 2,040,000, with a hemoglobin content of 30 per cent The Kahn reaction of the blood was negative The reaction of the stool to the benzidine test was positive on four occasions Gastric analysis revealed the presence of free hydrochloric acid in approximately normal amounts Roentgenologic examination showed the chest to be normal and there was no evidence of abnormality to the gastro-intestinal tract

The clinical diagnosis was bleeding peptic ulcer or possibly a bleeding carcinoma of the stomach After several transfusions his condition improved and a celiotomy was performed, June 24, 1931 The lower half of the stomach was found to be normal while in the upper half, posteriorly, there was a large mass about twice the size of a man's fist It extended upward to the diaphragm but was not adherent to it The tumor practically filled the omental bursa and was firmly attached posteriorly thus fixing the



Large neurogenic
sarcoma of posterior wall
of stomach invading retro-
peritoneal tissue

FIG 12—Case 4 J P Drawing illustrating a neurogenic sarcoma upon the posterior wall of the stomach which fills the lesser omental bursa and invades the pancreas

stomach to the vertebral column (Fig 12) On account of its position and size, removal seemed to be out of the question and accordingly with the electrosurgical loop, a small portion of the tumor was removed for biopsy

The postoperative convalescence was prolonged but on the whole was satisfactory There was one massive hemorrhage from the stomach, on the thirteenth postoperative day He was discharged from the hospital, July 25, 1931 He was last seen January 13, 1932, when he returned for check-up examination At that time his condition was essentially unchanged

Pathologic Examination—Microscopic The tumor is cellular neoplasm composed of spindle cells Certain areas show palisading Other areas have a cylindromatous architecture with whorl formation about blood vessels *Pathologic Diagnosis* The neo-

plasm is cellular enough to be considered a neurogenic spindle cell sarcoma arising upon a neurolemmoma

These case records demonstrate some of the problems involved in treatment. The first case was a neurolemmoma, adequately removed by a high subtotal gastrectomy, and the second, a similar lesion but one so situated as to require total gastrectomy. The third case was one of neurogenic sarcoma, dealt with by subtotal gastrectomy, while the last case was one of a far advanced, inoperable neurogenic sarcoma arising from the posterior gastric wall (Table V).

TABLE V
NEUROGENIC TUMORS OF STOMACH

<i>Treatment</i>	
Partial gastrectomy	2
Total gastrectomy	1
Exploration biopsy	1
Excision incidental	1
Removed—Resection for Ca (incidental)	2
	—
Total	7

Tumors of the Intestine, Colon and Rectum—In the portion of the digestive tract distal to the stomach, neurogenic tumors are extraordinarily rare. The reports of only a very few such lesions of the small intestine, colon and rectum are to be found in the literature. Stout, in his critical survey of the field in 1935, recognized the following cases as acceptable (Table VI).

TABLE VI
Author Location of Tumor

<i>Benign (neurolemmoma)</i>	
Delagéniere	Duodenum
Lemmonier and Peycelon	Duodenum
Kong	Small intestine
Leriche	Small intestine
Nordlander	Small intestine
Lhermitte and Leroux	Cecum
Peritz	Appendix
<i>Malignant (neurogenic sarcoma)</i>	
Adrian	Duodenum
Kohtz	Duodenum
Hartmann	Small intestine

At this time Stout believed that there was no case of neurogenic tumor of the colon or rectum which could be considered authentic.

T. S. Raiford²³ (1932) found no instances of neurogenic tumor in his study of 88 cases of tumors of the small intestine, from the Johns Hopkins Hospital material. Likewise Rankin and Newell²⁴ (1933) make no mention of such lesions in their review of 35 cases of benign tumors.

S A Goldberg²⁵ (1939) reported ten cases of unusual intestinal tumors. No neurogenic tumors other than one argentaffine tumor of the jejunum were included. Cohn, Landy, and Richter²⁶ (1939) reported seven cases of tumors of the small intestine, none of these being neurogenic in origin.

Geschickter¹² (1935), in his study of tumors of the digestive tract, found only ten neurogenic sarcomas among 962 malignant lesions. Three of these occurred in the small intestine and four in the rectum. He states that, microscopically, these tumors resemble the more common neurogenic sarcomas of peripheral nerves. In one of his cases, a tumor of the small intestine was associated with multiple subcutaneous nerve sheath tumors of the von Recklinghausen type. This author, also, in a discussion of his group of 178 benign tumors refers to a group of ten "lipomas, fibromas, and neuromas." The exact location of these lesions is not mentioned. More recent reports include the Cabot Case No. 24011,²⁷ and a case reported from the Mount Sinai Hospital by Klingenstein²⁸ (1938). The former was that of a 62-year-old male, who was found at operation, to have a neurogenic fibrosarcoma of the ileum. The clinical features of the case had been bleeding and the development of a pelvic tumor. The lesion which was described as being the size of the operator's fist, was successfully resected. Grossly, it resembled the leiomyomas found in the stomach, inasmuch as there was an area of deep ulceration in the mucosa over the central part of the tumor.

Klingenstein's patient was a 29-year-old female who had had repeated episodes of severe bleeding from the intestine, the cause of which proved to be an ulcerated neurofibroma of the ileum. The tumor was successfully resected.

Miller and Frank²⁹ (1939) reported two instances of neurofibrosarcoma of the intestine. The first was a 72-year-old female, whose only symptoms were those related to a pelvic tumor which proved, at operation, to spring from the jejunum. The tumor, a large extraluminal growth, was successfully resected. Microscopic study showed it to be a neurofibrosarcoma. The second patient, a 47-year-old male, complained only of weakness and vague abdominal pains. Celiotomy, and subsequently necropsy, revealed multiple tumors of the entire small intestine. These had produced partial intestinal obstruction in many places. The microscopic examination of all the lesions showed them to be neurofibrosarcomas.

Even more rare are the neurogenic tumors of the colon and rectum. Keith³⁰ (1937) reported the cases of a 50-year-old female, from whom a tumor, 1x2 cm, of the rectal wall was removed. The sections were examined by Doctor Ewing, who made a diagnosis of neurofibroma.

Woolf³¹ (1938) reported the case of a 70-year-old male, who was found to have a tumor lying between the rectum and the coccyx. Operation revealed that this arose in the rectal wall. The tumor was removed and histologic examination showed it to be a neurofibroma.

Glenn³² (1939) reported a case of neurogenic fibroma of the transverse

colon The patient was a 25-year-old female, who complained chiefly of frequency of urination and polyuria. An abdominal tumor was present which was localized to the transverse colon roentgenologically. It was successfully resected. Glenn states that, in a careful search of the literature, he was unable to find any other, microscopically verified, neurogenic fibroma of the colon.

In general, the clinical behavior of these tumors in the small intestine is similar to that of most benign tumors. If they are of the intraluminal type, intussusception is apt to occur or obstruction may be produced by virtue of their size alone. The extraluminal growths are usually manifested by the presence of an abdominal or pelvic tumor mass, possibly associated with pressure symptoms. Since there is often ulceration of the intestinal mucosa overlying the tumor, serious hemorrhages may occur, just as in the case of the gastric tumors.

Our series includes three examples of neurofibroma of the small intestine. The following case is one in which a solitary benign neurofibroma of the ileum was responsible for chronic intussusception (Fig. 13 A and B).

Case 5—I. K., white, female, age 60, a Finnish housewife, entered the hospital, October 30, 1939, complaining of abdominal pain and backache. Her symptoms began four months prior to admission. One month after the onset, a cervical polyp was removed elsewhere. Tissue examination showed no malignancy. She was not relieved and her symptoms had increased in severity, the pain localizing in the right lower quadrant. In addition, frequency of urination, urgency and nocturia had developed. Bimanual examination revealed in the anterior portion of the pelvis, and chiefly on the right side in the region of the bladder and extending out laterally, a cylindric, firm tumor mass which was very freely movable. Motion of this did not seem to impart any motion to the fixed uterus or cervix. Rectal examination was negative. The urine was normal. The Kahn test of the blood was negative. The leukocyte count was 7,500, and the hemoglobin content 70 per cent.

Roentgenologic studies showed (1) Normal colon, (2) normal upper gastro-intestinal tract, (3) faint visualization of the gallbladder, with at least one large nonopaque calculus. Thorough visualization of the urinary tract, including cystoscopy and retrograde pyelograms, yielded negative findings. A clinical diagnosis of a cyst or malignant neoplasm of the right ovary was made. A celiotomy was performed, November 18, 1939. At this time, a mass was noted in the midileum which proved to be an intussusception. This was reduced and a tumor about the size of an English walnut could then be palpated within the lumen of the bowel. A segment of ileum, approximately 25 cm in length, was resected and an end-to-end anastomosis performed. The postoperative course was stormy. On the tenth day a fecal fistula developed. On December 13, 1939, an attempt was made to close the fistula. This was unsuccessful. She developed general peritonitis and died, December 14, 1939. A necropsy was not obtained.

Pathologic Examination—*Gross* (Figs. 13 A and B) The specimen consisted of a segment of small intestine measuring 25 cm in length, with attached mesentery. Eight centimeters from one end, on a pedicle 1 cm long, there was an ovoid, firm, smooth mass, measuring 6.5 × 3.5 × 3 cm. The cut surface was pale, pinkish-gray, shiny, homogeneous, and moderately firm. There was considerable whorling. Some slight evidence of hemorrhage was noted at the distal end of the tumor and also at two points in the wall of the bowel.

Microscopic A loose textured, edematous neoplasm composed of Schwann cells and fibrous tissue in no characteristic arrangement. Much of the architecture is reticular in character. Many large, wavy, collagen fibers are seen throughout the neoplasm. *Pathologic Diagnosis* Neurofibroma.

NEUROGENIC TUMORS OF ABDOMEN

FIG 13 A



FIG 13 B

FIG 13 A—Case 5, I K Photograph of the segment of resected small intestine showing the intussusception
B—Case 5, I K Photograph of the large pedunculated neurofibroma which caused intussusception noted in Figure 13 A

The intestinal lesion in this case proved to be a large pedunculated neurofibroma. No history of bleeding was obtained.

The other two examples of neurofibroma of the small intestine in the series were discovered at necropsy and the intestinal lesion in these cases was but one of the local manifestations of a general neurofibromatosis. In one case, two small neurofibromas of the jejunum were found in a young man who had extensive plexiform neurofibromatous involvement of the prostate, periprostatic tissues, buttocks and left thigh. This case has been reported in detail elsewhere (McDonnell¹³). The other patient, a 15-month-old female, who died shortly after being admitted to the hospital, was found to have a congenital disturbance of the sympathetic nervous system with both angioneurofibromas and neurofibromas of the sympathetic nerves, involving the anterior and posterior mediastinum, celiac plexus, and the nerves of the small and large intestine (Fig 5). This was believed to be a form of von Recklinghausen's disease. No lesions on the surface of the body were noted. The abstracts of these two cases follow.

Case 6—G. H., white, male, age 30, a truck driver, was first seen in November, 1928, at which time he presented multiple subcutaneous nodules over the entire body. They were most marked on the posterior aspect of the thighs, the scrotum and the prepuce. The skin overlying these tumescences presented a diffuse, brown, macular eruption. There was an atrophic, undescended testis in the left inguinal canal. A diagnosis of von Recklinghausen's disease was made, and at this time the tumor mass on the posterior aspect of the left thigh was excised. Convalescence was uneventful. Microscopic examination of the tissue removed showed the lesion to be a congenital cirroid neurofibroma, or "fibroma molluscum." He returned in January, 1931, complaining of rectal pain due to pressure of the tumor masses in the left buttock. At this time, neurofibromas were removed from the left buttock and an anal plastic operation was performed. A circumcision was also performed in order to correct the phimosis due to the neurofibromatosis of the penis, the redundant foreskin being twice the length of the shaft. He again returned in July, 1935, because of acute urinary retention. He had been catheterized intermittently by his physician. He was semistuporous. The physical examination was essentially the same as on the previous admission except for the presence at this time of costovertebral tenderness. The bladder was considerably distended. The Kahn reaction of the blood was negative. The leukocyte count was 12,700, and the hemoglobin content 95 per cent. The urine contained albumin (three plus). There were many red and white blood cells as well as bacilli. The blood nonprotein nitrogen was 200 mg per cent, and the plasma chlorides were 331 mg per cent.

During his hospital stay, the bladder was gradually decompressed and continuous indwelling catheter, drainage was maintained. His general condition was so poor that diagnostic cystoscopy was not deemed advisable as a means of determining the cause of the vesical outlet obstruction. It was believed, however, that a vesical submucous neurofibroma similar to the cutaneous lesions might be responsible for the obstructive phenomena. His condition gradually grew worse, and he died, August 12, 1935.

Necropsy—The important findings were (1) Neurofibromatosis (von Recklinghausen's disease) (2) Extensive cirroid neurofibromatous infiltration in and about the prostate, prostatic urethra, bladder, seminal vesicles, and penis (3) Neurofibromas of the vagus and intercostal nerves and jejunum. There were two neurofibromatous nodules in the wall of the jejunum, each about 1 cm in diameter (4) Cirroid neurofibroma of the left buttock and thigh with scars of partial excision (5) Right nephrolithiasis (6) Ascending chronic purulent and ulcerative cystitis, ureteritis, and

pyelonephritis (7) Advanced pyonephrotic atrophy of both kidneys (8) Bilateral hematogenous, fibrinopurulent lobular pneumonia

Pathologic Examination—Microscopic The neoplasm in the jejunum is composed of Schwann cells with their anastomosing protoplasmic ramifications. Abundant fibrous stroma. Dispersed throughout the tumor are irregularly-shaped hyalin bodies simulating those seen in meningiomas. *Pathologic Diagnosis* Neurofibroma. *Prostate* Throughout the prostate and periprostic tissues is a diffusely infiltrating plexiform neurofibroma.

Case 7—D. G. white, female, age 15 months, was brought to the hospital, July 19, 1930, because of weakness, emaciation, and marked pallor. The mother stated that this condition had been present since shortly after birth. She was a "blue baby" and one of twins. Examination revealed cardiac enlargement, and an enlarged liver. Temperature 103° F. The Kahn reaction of the blood was negative. The leukocyte count was 13,000, with 55 per cent polymorphonuclear leukocytes, the erythrocyte count 1,700,000, and the hemoglobin content 18 per cent. A blood transfusion was administered at once. Her condition grew rapidly worse and she died that evening.

Necropsy—(1) Congenital disturbance of the sympathetic nervous system probably related to von Recklinghausen's disease. Multiple knotted, twisted, grape-like masses along course of the vagus nerves and celiac plexus. Knotted mass in posterior mediastinum 4.5×3.5×1 cm. in diameter. Throughout the small and large intestines are multiple, small conglomerate, purplish nodules, some of which hang free in the intramesenteric fat. Some are firmly attached to the intestinal wall and appear to lie between the muscularis and the mucosa. (2) Extreme congestion of lungs and brain. (3) Fibroid atrophy of thymus. (4) Fatty liver. (5) Patent ductus arteriosus and foramen ovale. (6) Horseshoe kidney with double ureter.

Pathologic Examination—Microscopic (Fig. 5) The multiple tumor masses are composed of angiomatous and angioneurofibromatous masses of young nerve sheath tissue. Typical Schwann cells can be seen as demonstrated by Masson's trichrome and Mallory's phosphotungstic acid hematoxylin stains. An abundant amount of reticulin and fibrous tissue is noted within the neoplasms. *Pathologic Diagnosis* Multiple neurofibromas of small and large intestines.

In one of the three cases of neurogenic sarcoma exhibiting metastases, a large primary lesion was found in the pelvis (Case 18). The diagnosis of neurogenic sarcoma was made from tissue obtained from a rectal biopsy. Since death occurred a few weeks later from exsanguination due to massive hemorrhages from the rectum, it is entirely possible that this tumor arose from the rectal wall, yet positive proof is lacking and in view of the rarity of such tumors in the rectum, the case has been placed in the retroperitoneal group.

Tumors of the Mesenteries—As previously mentioned, tumors of the type under discussion are frequently found in unusual or out-of-the-way places. Examples of such odd situations are the mesenteries and omenta. Since Rankin and Major³⁴ were able, in 1932, to report 22 cases of tumors of the mesenteries and cite several hundred similar cases in the literature, it is evident that mesenteric tumors are not excessively rare. Wallen and Sommer,³⁵ in a study of sarcoma of the soft parts, found 63 neurogenic sarcomas, four of which were in the abdominal region. One of these was situated in the mesentery. Further details of the case are not given. Moreover, instances of tumors of the greater omentum are reported from time to time. Nevertheless, the fact that in our small series of 18 nerve sheath tumors

(four of which were merely incidental findings) there should be two tumors in such locations would seem to be of some significance. One of these cases was a huge neurolemmoma arising in the gastrocolic omentum, and the second was a neurogenic sarcoma developing in the mesentery of the terminal ileum. The abstracts of these cases are appended.

Case 8—G. K., white, male, age 43, a Canadian salesman, entered the hospital, July 22, 1937, with the complaint of pain in the left upper quadrant and a tumor mass in the abdomen. One month previously, because of vague abdominal discomfort, he consulted a physician, who discovered the mass in the upper abdomen. There had been no change in bowel habit, no abnormalities of the stools, and no weight loss. Examination disclosed a globular, slightly tender and slightly movable mass about the size of a grapefruit situated in the epigastrium. The urine was normal. The Kahn test of the blood was negative. The leukocyte count was 8,500, with 70 per cent polymorphonuclear leukocytes, the erythrocyte count, 5,470,000, and the hemoglobin content 107 per cent. The blood bilirubin was 4 mg per 1,000 cc and the fasting blood sugar was 72 mg per cent. Roentgenologic studies revealed (1) A normal chest, (2) normal gallbladder visualization without stone, (3) normal colon, (4) no intrinsic gastric or duodenal lesion but evidence of pressure from a large extra-alimentary tumor possibly arising in the pancreas (Fig 14B). The preoperative clinical diagnosis was pancreatic or omental cyst.

A celiotomy was performed, July 26, 1937. The tumor was found to be solid in character and to have arisen in the gastrocolic omentum. It involved a portion of the greater curvature of the stomach and also the transverse colon (Fig 14A). Complete removal was accomplished by resecting the lower half of the stomach by the Polya method and by an obstructive resection of the involved segment of the transverse colon. Convalescence was uneventful and he was discharged from the hospital, August 14, 1937. He returned to the hospital, October 6, 1937, and a closure of the temporary colostomy, resulting from the obstructive resection of the colon, was performed. Again the convalescence was uneventful, and he was discharged, October 26, 1937. He was last seen, June 2, 1938. He was free from symptoms, and entirely well except for a slight ventral hernia in the surgical scar.

Pathologic Examination—Gross. The specimen consisted of a portion of omentum, measuring 27×22 cm, in which there was a firm, round, encapsulated mass measuring 14×8×6 cm. This mass was attached to the wall of a segment of stomach 9 cm in length. The mucosal surface was smooth and not infiltrated. On the opposite side of the tumor was attached a segment of colon 7 cm in length.

Microscopic. A large neoplasm showing whorling and interlacing cords of cells. Areas of palisading noted. Much of the tumor is reticular in structure (Fig 2B). Masson's stain demonstrates the special histologic characteristics of a nerve sheath tumor.

Pathologic Diagnosis. Neurolemmoma.

Case 9—D. E., white, male, age 52, a mail carrier, was first seen November 8, 1937, complaining of pain in the abdomen. Three years previously he had had an appendectomy for right lower quadrant pain. Following this he was well for a year, whereupon he again developed sharp pains in this same region. In June, 1937, a mass was discovered in the lower abdomen. Shortly after this he experienced an attack of intestinal obstruction, which was relieved by nonoperative measures. There had been no melena or hematemesis. The tumor mass had gradually increased in size and there had been a slight weight loss.

Physical examination revealed a firm, nontender, movable mass, measuring approximately 6×6 cm, in the right lower quadrant. Rectal examination was negative. The urine was normal. The leukocytes numbered 11,000, with 68 per cent polymorphonuclear leukocytes, and the erythrocytes 4,200,000, the hemoglobin content was 68 per cent. A barium enema showed no intrinsic lesion of the colon. The preoperative, clinical diagnosis was probable abdominal lymphoblastoma.

NEUROGENIC TUMORS OF ABDOMEN

Operation was performed, November 19, 1937 In the mesentery of the terminal ileum near the cecum was a large rounded mass, slightly nodular on its surface, lying between the peritoneal leaves It measured approximately 15x8 cm There were also

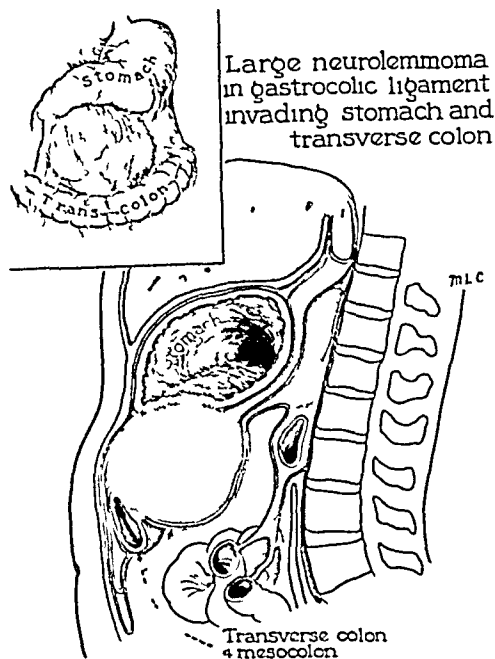


FIG 14 A—Case 8 G K Drawing illustrating a large neurolemmoma of gastro colic ligament (Fig 2 B) invading the stomach and transverse colon

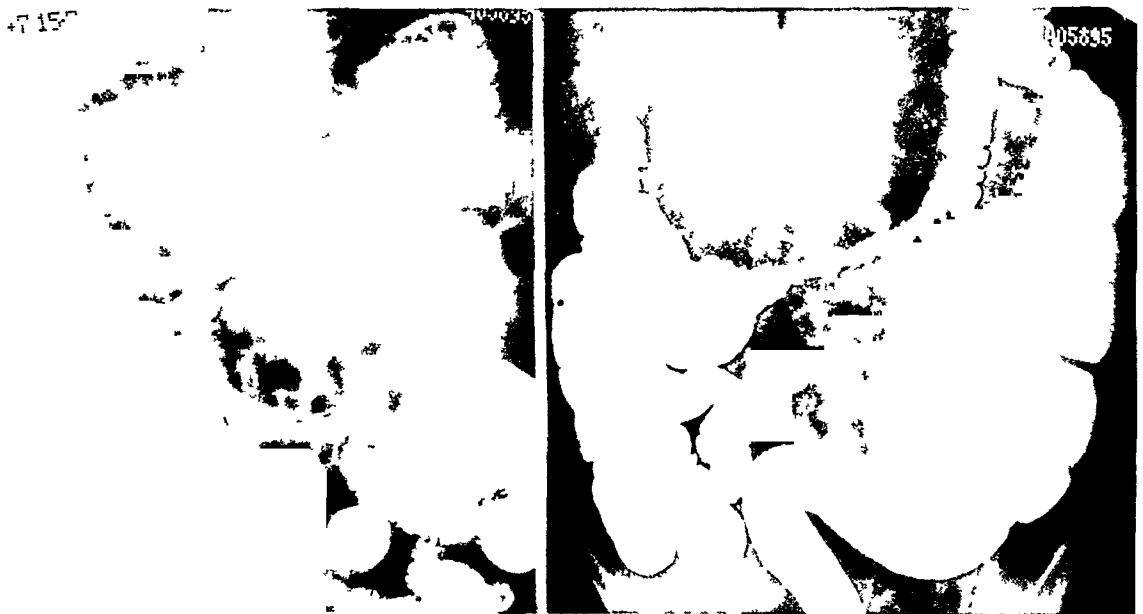


FIG 14 B—Case 8, G K Roentgenographic appearance of the neoplasm illustrated in Figure 14 A demonstrating the arch formed by the stomach, duodenum and transverse colon about the tumor mass

several enlarged lymph nodes in the mesentery The tumor was quite movable and could be delivered into the wound At both ends of the mass the small intestine was firmly adherent to it The tumor was excised and short segments of intestine at the two ends resected with end-to-end anastomoses The postoperative convalescence was stormy, and the clinical picture was that of general peritonitis He died, December 6, 1937

Necropsy revealed complete gangrene of the small bowel and its mesentery. Metastases of the neoplasm were found in the liver and on the subdiaphragmatic peritoneum.

Pathologic Examination—Gross The specimen consisted of a large nodular tumor mass, which measured 15×8×7 cm. Two segments of small intestine, measuring 10 cm in length at one end and 9 cm in length at the other, were intimately attached to the tumor mass. The mass appeared to arise within the mesentery but had involved the intestinal wall at one point (Fig 15).



FIG 15—Case 9 D E Photograph of a large nodular mesenteric neurogenic sarcoma which had invaded two segments of small intestine. Hepatic metastases were demonstrated at necropsy (Fig 8).

Microscopic A cellular neoplasm composed of elongated spindle cells, arranged in both interlacing cords and whorls. Other parts of the tumor are composed of reticular areas. Mallory's phosphotungstic and hematoxylin stain demonstrates the spindle cells, with large oval, plump blue-staining nuclei with a scant amount of pinkish-brown-staining cytoplasm which extends at both ends into cytoplasmic ramifications which appear to anastomose with similar fibrillae from adjacent cells. These fibrillae appear to be ensheathed in orange, collagenous material. *Pathologic Diagnosis* Neurogenic sarcoma arising in a neurolemmoma. Metastasis in liver. *Microscopic* It will be noted that by comparing the hepatic metastasis with the primary neoplasm that the metastatic lesion is definitely more cellular. The cells are shorter and more plump. The reticulin is seen with difficulty. There are areas that are suggestive palisading (Fig 8). *Pathologic Diagnosis* Metastatic neurogenic sarcoma.

The first case is practically identical with the one reported by Schrager³⁶

(1939) His patient was a 40-year-old female, who also presented herself for examination on account of a large abdominal tumor. It was removed by an operative procedure similar to that described above. The case affords a good example of the involvement of adjacent viscera by a neurolemmoma (Fig 14 A). While an operative procedure of considerable magnitude was necessary in order to insure complete removal of the tumor, an excellent result was obtained. In view of the benign character of the lesion as indicated by the histologic studies, further trouble on this score seems unlikely. Clinically, our case was also of interest in showing how such a neoplasm may be present for a long period of time, and reach a large size, and still provoke relatively few symptoms.

The second case illustrates some of the technical difficulties attendant upon removal of large tumors of the mesentery (Fig 15). This case was one of three in the series in which distant metastases from a neurogenic sarcoma were found.

Tumors of the Retroperitoneal Tissues—Retroperitoneal tumors are not especially rare and many types of tumors found in this location have been described. This great variety of lesions can be readily understood by considering the various retroperitoneal tissues which may give rise to new growths. These include connective tissues, blood vessels, lymphatics, lymph nodes, fat, and the various structures of the sympathetic nervous system. While many of the tumors such as the lymphoblastomas, the teratomas and the neuroblastic tumors of the sympathetic nervous system are quite hopeless, there is a considerable number of retroperitoneal tumors which are benign or tend to be of local malignancy only, and hence amenable to surgical attack. To this latter group belong the majority of the nerve sheath tumors. That the neurogenic tumors constitute but a small percentage of the total number of retroperitoneal new growths is evinced by the fact that they are not mentioned in the communications on this subject by Trout and Meekins,³⁷ or Hansmann and Budd.³⁸ Judd and Larson³⁹ (1933) reported 48 retroperitoneal tumors from the Mayo Clinic. Only one of these was of neurogenic origin—it being a paraganglioma which had developed in the suprarenal gland, a type of tumor beyond the scope of the present paper. Unusual cases of nerve sheath tumors in this region, cited by Stout, are those of Virchow, Eichhoff, Pescatori, Erb, Frank, Kiekeley and Krumbein, Moreau and van Bogaeit, and Pana.

Warren and Sommer³⁵ found two of their four abdominal neurogenic sarcomas to be situated in the retroperitoneal space, while one was described as being in the pelvic region, and probably should also be included here.

Frank⁴⁰ (1938), in a splendid review of the subject, has summarized the literature and has tabulated the important data concerning 107 tumors found in the literature from 1925 to 1932. He carefully excludes tumors arising from abdominal organs (liver, pancreas, adrenals, intestines, genital or urinary organs) as well as mesenteric and omental growths. Also, neoplasms arising from residual urogenital embryonic rests are not considered. Frank's com-

piled group contains 20 neurogenic retroperitoneal tumors, or 18.7 per cent of the total. On the basis of histologic classification, these 20 tumors fall into the following groups: (a) Neurinoma—seven, (b) neurogenic sarcoma—three, (c) ganglioneuroma—six, (d) sympathoblastoma—four. It is only with the first two types that the present discussion is concerned. The operative mortality in this collected group of 20 tumors was 22 per cent, in contrast with no deaths in the group of 28 benign fibromas, lipomas, cysts, *etc.*, and a 28.13 per cent mortality for the general group of sarcomas (38 cases).

In the present series of cases, there were six neurogenic tumors of the retroperitoneal space. Of these, there were four neurogenic sarcomas, one neurolemmoma, and one ganglionated neurofibroma. Surgical removal was possible in four instances, the extirpation, apparently, being complete in two cases, whereas in the other two it was necessary to leave a portion of the base of the tumor due to its proximity to important structures such as the great vessels, bladder or rectum. In the remaining two cases, only a small amount of tissue for biopsy purposes was removed. In one instance (Case 18) this was secured by means of proctoscopy, from a lesion involving the rectal wall, and in one (Case 17), tissue was obtained at the time of an exploratory celiotomy for what proved to be an inoperable retroperitoneal neurogenic sarcoma with extensive metastases to the mesenteric lymph nodes.

The two following cases are of special interest because of the remarkable roentgenologic and operative findings in one, and the unusual clinical history in the other.

Case 10—E. J., white, male, age 47, a laborer, was first seen, June 15, 1933, complaining of constipation, nervousness, nausea and vomiting. For one year he had noticed increasing constipation. For the past six months he had been troubled with abdominal distention, much flatus, and increasing weakness. Following meals there had been a dull pain in the right upper and the left lower quadrants of the abdomen with occasional vomiting spells. He had lost a considerable amount of weight.

Physical examination showed marked pallor of the skin and mucous membranes. A mass was felt which seemed to arise from the pelvis and extend upward almost to the umbilicus and laterally to the outer borders of the rectus muscles. This mass was tympanic to percussion. There was moderate tenderness over this area. The liver was enlarged. The mass could barely be felt on rectal examination. Sigmoidoscopic examination was negative. Laboratory studies showed the urine and stool to be normal. The leukocyte count was 5,700, with 79 per cent polymorphonuclear leukocytes, the erythrocyte count 3,000,000 with a hemoglobin content of 35 per cent. The red cells showed achromia. The Kahn test of the blood was negative. Roentgenologic examination revealed: (1) No organic lesion of the upper alimentary tract, (2) fistulous communication between small bowel and encapsulated right-sided pelvic abscess, (3) no intrinsic lesion of the colon, (4) foreign body, probably lead shot, within pelvic mass (Fig. 16 B). A clinical diagnosis was made of a pelvic abscess communicating with the small intestine probably due to neoplasm or diverticulitis.

Operation was performed, September 13, 1933. At this time a large tumor was found which was thought to be a sarcoma arising from the pelvis. The upper portion was fairly mobile. At the apex of the mass a loop of small intestine was firmly adherent, and this proved to be the point of communication between the abscess cavity and the bowel, as had been indicated roentgenologically. The tip of the appendix was also adherent to the tumor. At the base of the tumor in the pelvis, posterior to the bladder, the attach-

NEUROGENIC TUMORS OF ABDOMEN

ments were extremely firm, and accurate isolation of structures was impossible (Fig 16 A) In order to mobilize the tumor, the involved coil of intestine was resected and the appendix also removed with the mass Deep in the pelvis the tumor was so firmly

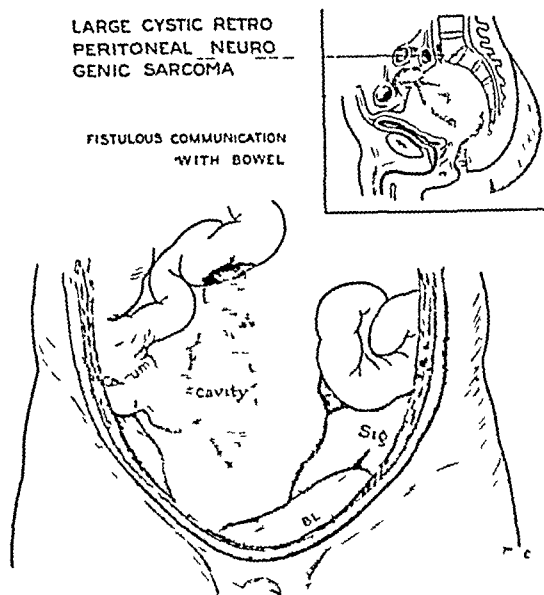


FIG 16 A—Case 10, E J Drawing illustrating a large cystic retroperitoneal neurogenic sarcoma having a fistulous communication with the small intestine

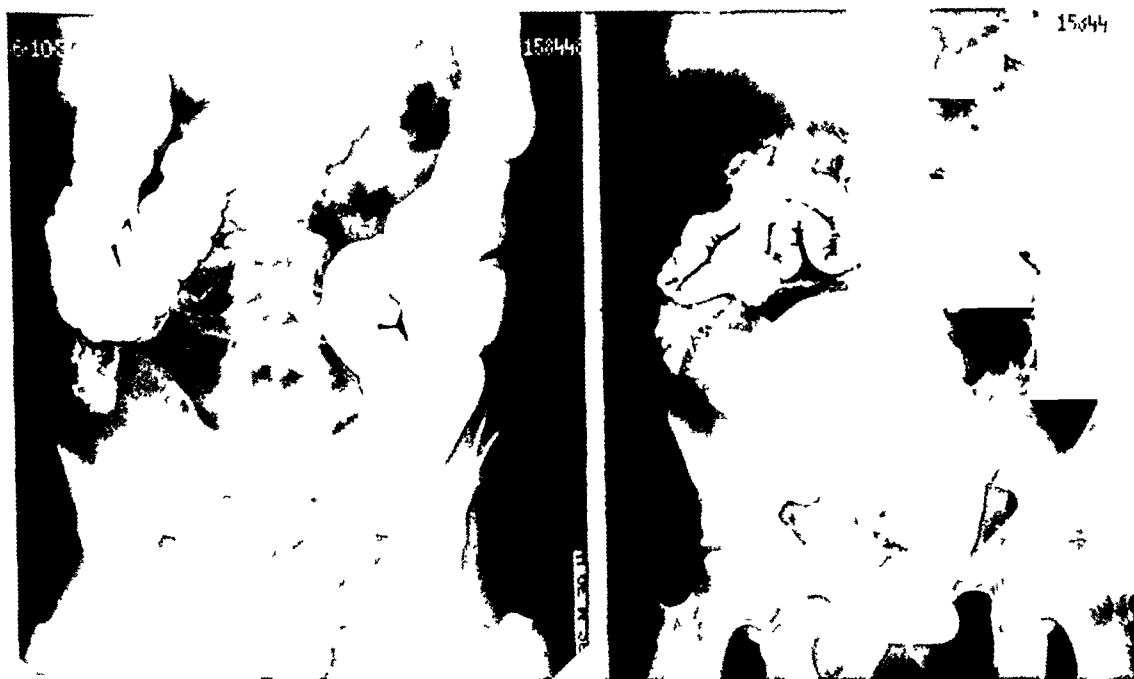


FIG 16 B—Case 10, E J Roentgenologic examination, following a barium enema, June 10, 1933, reveals the displacement and compression of sigmoid colon, indicating a large extra alimentary tumor mass upon the right side of the pelvis and abdomen, as shown in drawing, Figure 16 A Roentgenologic examination, September 6, 1933, demonstrates a fistulous communication between the small intestine and barium filled cystic space, which was interpreted as an abscess A small opaque object is noted upon the floor of the cystic space

fixed that complete excision was impossible Accordingly, the greater part of the tumor was removed, leaving a small portion of the base behind the bladder Convalescence was slow but satisfactory He was discharged from the hospital, November 9, 1933 He was subsequently given a course of deep roentgenotherapy to the pelvis Following this he

remained in fair health, gradually gaining in weight, and was last seen, April 19, 1935, at which time there was no demonstrable evidence of recurrence or metastasis. Later in the year both legs became paralyzed and he died, September 22, 1935.

Pathologic Examination—*Gross* The specimen consisted of a hollow tumor mass, the wall of which had been ruptured. The central cavity was lined by an ulcerating, fungating mass of neoplasm which was covered with a thick, foul exudate. The appendix was attached and also a segment of small intestine, the lumen of which communicated directly with the cavity in the tumor.

Microscopic A cellular neoplasm composed of spindle cells showing areas of less complete differentiation in which the cells are polyhedral in form. Other, more differentiated, areas show persistence of original architecture in which there are palisading and whorl formation about the blood vessels resembling a neurolemmoma. Perdrau's silver stain demonstrated a fine reticular structure throughout, Masson's trichrome technic, and Mallory's phosphotungstic acid hematoxylin stains substantiate the nerve sheath origin of this neoplasm. There is infiltration of the intestinal wall with ulceration of intestinal wall and neoplasm on side exposed to intestinal content. *Pathologic Diagnosis* Neurogenic spindle cell sarcoma.

Case 11—J. S., white, age 49, a fireman, was first seen, February 8, 1938, because of pain in the right leg. This was first noticed about seven years previously. The pain had been most severe on the anterolateral aspect of the thigh. It varied in intensity from a very sharp and severe type to a dull ache, lasting from several minutes to an hour. The attacks of pain occurred every two or three months at first but more recently had increased in frequency. He had noticed little if any weakness in the right leg. In 1927, a diagnosis of syphilis had been made and, at that time, he received an intensive course of antiluetic therapy. The positive physical findings were as follows: (1) Atrophy of the anterior thigh muscles on the right with definite weakness of the iliopsoas. (2) Mild weakness in the right adductors and quadriceps. (3) Right cremasteric reflex diminished. (4) Right knee jerk very weak, left normal. (5) Mild hypesthesia on the right side from L1 to L4 and on the left in L1 and L2. The blood Kahn test was doubtfully positive. The uranalysis was normal and the blood count normal. The cerebrospinal fluid was normal. Roentgenograms of the spine showed a moderate degree of hypertrophic arthritis of the lower dorsal and upper lumbar spine, while the right knee and the chest were normal. Studies of the gastro-intestinal tract and of the urinary tract revealed no abnormalities. Intraspinal lipiodol injection revealed a temporary hesitation of lipiodol at the level of the twelfth and eleventh dorsal vertebrae at which point the lipiodol dispersed into droplets. The findings were interpreted as evidence of a moderate degree of arachnoiditis at the lower dorsal region and the presence of a cord tumor was considered very unlikely. During his stay in the hospital his symptoms improved under bismuth antiluetic therapy. A plaster of paris body encasement was applied to provide complete rest, and he was discharged, March 12, 1938.

He returned, June 8, 1938, at which time his symptoms were as severe as ever. Exploratory laminectomy was advised and performed, June 12, 1938. At this time, no abnormalities of the spinal cord or nerve roots could be ascertained. The posterior divisions of the twelfth dorsal and first and second lumbar spinal nerves were sectioned on the right side. His convalescence was uneventful, and there was slight improvement of his symptoms. In view of the incomplete relief a cordotomy was performed, June 24, 1938. The result of this was fairly satisfactory.

He was next seen, in February, 1939, at which time he complained of a mass in the right lower quadrant of the abdomen. He had lost considerable weight. The mass was easily palpable and seemed quite firmly fixed. Roentgenologic studies of the colon at that time revealed that this was not an intrinsic lesion of the colon, and that the colon was displaced medially. A diagnosis of a retroperitoneal tumor was made and he was operated upon, February 7, 1939. At the time of the celiotomy no significant findings were noted other than a retroperitoneal mass in the right lower quadrant. The posterior

peritoneum was incised and the tumor removed without difficulty. Convalescence was uneventful and he was discharged, February 21, 1939. He was last seen, September 27, 1939 when he was entirely free from pain, showed great improvement in his general health, and examination revealed no signs of recurrence.

Pathologic Examination—Microscopic (Fig. 3) A well circumscribed edematous tumor composed of Schwann cells, in an arrangement characteristic of Antoni's Type B reticular tissue. Masson's trichrome stain beautifully demonstrates the pink Schwann cells with their protoplasmic ramifications in a syncytial network, each fibril being ensheathed in a thin capsule of bluish-green-staining collagen. Peirce's silver stain demonstrates the argyrophilic reticulum with large, wavy bands of collagen irregularly dispersed throughout. *Pathologic Diagnosis* Neurolemmoma.

The tumor in the first case evidently arose in the retroperitoneal or subperitoneal space, becoming wedged in between the bladder and rectum as it increased in size. Neoplastic infiltration of the wall of a loop of small intestine which had become adherent to the mass took place with subsequent perforation and the development of a fistulous communication between the intestinal lumen and the central cystic cavity of the tumor. Removal of the tumor required a resection of the involved segment of small intestine as well as removal of the appendix which was likewise incorporated in the mass (Fig. 16 A).

In view of the incomplete removal of the tumor, postoperative roentgen treatments were given even though their value was problematic.

The second patient had a long and complicated history and presented a most difficult diagnostic problem. It was not until the abdominal tumor finally became palpable that a correct diagnosis of retroperitoneal tumor was made. The ease of the surgical removal, the benign character of the neoplasm and the marked clinical improvement following removal are matters worthy of note.

The ganglionated neurofibromas should be distinguished from the more common ganglioneuromas, which properly belong to the neuroblastic tumors of the sympathetic nervous system. Our series contained one example of a ganglionated neurofibroma. It was a retroperitoneal tumor situated in the lumbar region just to the left of the midline and occurred in a four-year-old girl. The ganglionated neurofibromas are in fact benign nerve sheath neoplasms which develop in the neighborhood of sympathetic ganglia. As growth of the tumor takes place, ganglia cells become included. Their rôle is entirely passive. The cells are the mature forms and they do not lend malignant characteristics to the lesion (Fig. 6). Similar tumors in the thorax have been mentioned by Andrus,¹¹ who points out the fact that these tumors are composed of fibrous tissue in the midst of which ganglion cells can be demonstrated. He suggests that it is only by virtue of their situation or point of origin that the ganglion cells are found. The clinical course, treatment and prognosis are essentially the same as in the case of a neurofibroma or neurolemmoma in the same position.

Case 12—J. S., female, aged six, was brought to the hospital by her parents, March 21, 1930, because of a mass in the abdomen. This had been discovered six months

previously during a routine physical examination, and had produced no symptoms. Examination showed the superficial veins of the abdominal wall to be prominent. There was a mass in the left lower quadrant which measured approximately 12x7.5 cm. It was smooth, firm and fixed. It was not lobulated and not tender. Examination of the urine and stool was negative. The leukocyte count was 11,300, the erythrocyte count 4,210,000, and the hemoglobin content 85 per cent. The Kahn reaction of the blood was negative. Roentgenologic studies of the chest, upper gastro-intestinal tract and colon were negative. A diagnosis of retroperitoneal sarcoma was made.

A celiotomy was performed, April 9, 1930. A tumor measuring roughly 7.5x7.5x7.5 cm was found closely attached to the lateral aspect of the second, third and fourth lumbar vertebrae. The large vessels were close to it. It was found impossible to remove all of the tumor. Consequently, the pedicle was left *in situ*. It would have been impossible to remove this without ligating the vena cava. Convalescence was uneventful. Postoperative deep roentgenotherapy was instituted, and she was discharged from the hospital, May 10, 1930. She was last seen in April, 1940, at which time she was in good health and was developing normally. There was no evidence of recurrence.

Pathologic Examination—Microscopic (Fig. 6) A large encapsulated neoplasm composed of adult sympathetic ganglion cells in an irregularly arranged schwannian and fibrous stroma which appears reticular and edematous in areas, as demonstrated by Masson's trichrome blue and Mallory's phosphotungstic acid stains. *Pathologic Diagnosis* Ganglionated neurofibroma.

ADDITIONAL CASE ABSTRACTS

Neurogenic Tumors of the Stomach

Case 13—J. D., white, female, age 55, a housewife, entered the hospital, February 16, 1940, complaining of pain in the side and a draining abdominal sinus. Five years previously, following a typical attack of gallstone colic, a cholecystostomy had been performed elsewhere. Many stones were removed from the gallbladder. Four years later, an abscess developed in the scar. This was drained, and since that time there had been persistent drainage of small amounts of clear serous fluid but sufficient in quantity to require constant dressing.

Physical examination revealed a well-healed surgical incision, 12 cm long, in the right upper quadrant. At the upper angle there was the opening of a small sinus, covered with a crust. There was a large ventral incisional hernia. Laboratory studies showed the urine to be normal, the Kahn reaction of the blood to be positive three plus, and the reaction of the stool to the benzidine test to be positive four plus. The leukocyte count was 7,500, the erythrocyte count 4,850,000, and the hemoglobin content 76 per cent. Roentgenologic studies demonstrated no evidence of an intrinsic lesion of the gastro-intestinal tract other than slight gastric retention at the end of five hours. There was nonvisualization of the gallbladder and no evidence of gallstones.

A diagnosis of recurrent cholelithiasis with occlusion of the cystic duct was made and celiotomy performed, February 20, 1940. A fairly large gallbladder was found which contained white bile but no stones. An exploratory choledochostomy revealed no stones in the common duct. The gallbladder was removed. On the anterior surface of the stomach a small pedunculated tumor was noted. This was about the size of a walnut. It was thought to be a benign tumor and was removed. Convalescence was uneventful and she was discharged from the hospital, March 14, 1940.

Pathologic Diagnosis—Gross (1) The gallbladder was 9 cm and practically intact. There were numerous adhesions with considerable thickening of the wall. No stones were present. (2) The specimen from the stomach consisted of a smoothly lobulated, solid piece of tissue measuring 3x2.5x1.5 cm.

Microscopic (1) Old chronic purulent cholecystitis. Marked fibrosis of the gallbladder wall. (2) Hematoxylin-eosin stain demonstrates a cellular neoplasm showing

short, plump spindle cells with round and oval nuclei. Architecture is that of interlacing bands and whorls of spindle cells. Perdrau's silver stain shows a fine reticulum throughout the tumor. *Pathologic Diagnosis* Neurogenic sarcoma.

Case 14—F M, white, male, age 61, a lawyer, entered the hospital, June 30, 1939, complaining of pain in the upper abdomen associated with nausea and vomiting. The symptoms began only five weeks previously. There had been no hematemesis or melena. Since the onset of his trouble his appetite had been poor, and there was a sense of fullness in the stomach following the ingestion of food. There had been a weight loss of 15 pounds (6.8 Kg). Examination disclosed an ill-defined mass in the midepigastrium which was slightly movable. Urinalysis showed the presence of 20-30 white blood cells per low power field, and a stained smear of the sediment showed many cocci. The Kahn reaction of the blood was negative. The leukocyte count was 8,700, and the erythrocyte count 4,400,000. The hemoglobin content was 78 per cent. Roentgenologic examination revealed an extensive annular neoplasm involving the lower third of the stomach, and normal visualization of the gallbladder by the Graham-Cole test.

A celiotomy was performed July 3, 1939. A carcinoma was found involving the lower third of the stomach. There was no gross evidence of spread. The adjacent lymph nodes were moderately involved but not extensively so. A partial gastrectomy was performed according to the Hofmeister technic. The postoperative convalescence was uneventful and he was discharged from the hospital, July 21, 1939.

Pathologic Examination—*Gross* The specimen of the stomach measured 13 cm in length. Three centimeters from the distal amputation side, on the greater curvature in the prepyloric portion, was a 4x3.5 cm raised, nodular mass with slight ulceration of the surface. It infiltrated through the serosa. At some distance from this lesion, and on the serosal surface was a smooth, ovoid mass, measuring 2x1x1 cm, which was whitish in color and very firm in consistency.

Microscopic (1) Adenocarcinoma mucosum, Grade II, primary in gastric mucosa. Ulcerating surface. The carcinoma infiltrates entirely through the wall. Numerous signet-ring cells. (2) A neoplasm composed of an edematous architecture of Schwann cells with areas arranged in interlacing bands and whorls characteristic of a neurolemmoma. Slight increase in amount of connective tissue stroma. *Pathologic Diagnosis* Neurolemmoma.

Case 15—E H, white, female, age 66, a housewife entered the hospital, August 2, 1935, complaining of weakness and loss of weight. Her symptoms were of six months' duration. The physical examination was essentially negative except for a questionable mass in the epigastrium. Laboratory examinations showed the urine to be normal. The leukocyte count was 12,800, with 72 per cent polymorphonuclears, the erythrocyte count 4,820,000, and the hemoglobin content 65 per cent. The Kahn test on the blood was negative. Roentgenologic studies showed a partially obstructing lesion involving the distal third to half of the stomach, which was believed to represent carcinoma.

Operation was performed, August 6, 1935. A carcinoma involving the antral portion of the stomach was found. The growth extended 3.5 cm upward from the pylorus. It involved nearly the entire circumference of the stomach at this point. There were no definitely enlarged lymph nodes along either the greater or the lesser curvatures. Both lobes of the liver, the spleen and gallbladder were normal. The lower half of the stomach was resected by the Pólya method. Postoperative convalescence was uneventful. She was discharged from the hospital, August 24, 1935. She died at home in March, 1937.

Pathologic Examination—*Gross* The stomach measured 12x9x4 cm. At one end of the specimen the mucosa presented an ulcer 5x3.5x3 cm. The edges were rolled and everted. At the opposite end of the specimen on the serosal surface was a small tumor 2.5x2x1.5 cm on a narrow pedicle.

Microscopic (1) A well advanced adenocarcinoma infiltrating through the stomach wall into the subserosa. (2) A neoplasm composed primarily of Antoni's Type B reticular tissue. Histologically, small spindle cells with an occasional polyhedral form.

are noted, both of which have anastomosing cytoplasmic end processes and are surrounded by a fibrillar network *Pathologic Diagnosis* Neurolemmoma

Retroperitoneal Neurogenic Tumors

Case 16—R B, white, male, age 28, a Jewish lawyer, was first seen, March 21, 1928, complaining of a mass in the abdomen. This had been discovered about four years previously. It had caused no symptoms, and there had been no appreciable increase in size. Examination revealed a mass approximately 7.5x6 cm in the lower abdomen lying near the midline. It extended from 3 cm above the symphysis to the umbilicus. It was quite firm to palpation and was slightly movable. Laboratory examinations showed the urine to be normal, the leukocyte count 11,600, and the hemoglobin content of the blood 95 per cent. The Wassermann reaction of the blood was negative. The clinical diagnosis was retroperitoneal sarcoma.

Celiotomy was performed, March 28, 1928. Exploration revealed an egg-shaped tumor 15x7.5 cm lying in front of the promontory of the sacrum between the iliac vessels and in the root of the mesentery of the small intestine. The posterior peritoneum was incised and the tumor easily, and apparently completely, removed. Following operation the convalescence was uneventful except for a slight wound infection. He was discharged from the hospital, April 12, 1928. Subsequently, a course of deep roentgenotherapy was administered. When last heard from, October 22, 1932, his health was excellent and his recovery had been complete.

Pathologic Examination—Microscopic A neoplasm characterized by interlacing cords and whorls of Schwann cells. Certain areas show evidence of palisade formation. Throughout the neoplasm are seen large wavy collagen fibers. Portions of the neoplasm are becoming cellular enough to be considered sarcomatous. Not likely to metastasize. *Pathologic Diagnosis* Neurogenic sarcoma.

Case 17—R H, white, male, age 37, an American farmer, entered the hospital, February 17, 1939, with a chief complaint of indigestion and pain in the abdomen and back. The symptoms had begun two years previously with vague generalized abdominal pain coming on following meals. For about a year he obtained considerable relief on an ulcer dietary regimen, after which time pain and indigestion recurred. Since then, except for periods of temporary relief, he had grown steadily worse. He had lost about 50 pounds (22.7 Kg) in weight, and had become so weak that he had to give up his work. There had been no nausea, vomiting, or melena. Physical examination revealed a slightly tender, hard, nodular, fixed mass, 7.5x5 cm, in the midepigastrium. The laboratory studies showed a normal urine, and a negative Kahn reaction of the blood. The leukocyte count was 6,000, with 64 per cent polymorphonuclear leukocytes, the erythrocyte count 5,300,000, and the hemoglobin content 86 per cent. Examination of the stool revealed a positive two plus reaction to the benzidine test. Gastric analysis and a glucose tolerance test showed normal values. Roentgenograms showed a normal upper gastro-intestinal tract, normal visualization of the gallbladder, without evidence of included stone, and a normal chest. The barium sulphate enema demonstrated a redundant colon but no evidence of an intrinsic lesion. The clinical diagnosis was retroperitoneal tumor.

Celiotomy was performed, March 3, 1939. The spleen, liver and gallbladder were normal. The stomach, duodenum and kidneys were also normal. The retroperitoneal space, in the midline, was occupied by an extensive, hard, fixed, nodular mass. In the root of the mesentery of the small intestine a number of enlarged, hard lymph nodes were felt. Resection was impossible and no palliative procedure seemed to be indicated. Two bits of tissue were removed for biopsy. The postoperative course was uneventful, and he was discharged, March 20, 1939. He died at home, December 6, 1939.

Pathologic Examination—Microscopic A very cellular neoplasm composed of coiled columns of Schwann cells giving a palisaded appearance. The histologic characteristics of this neoplasm are best illustrated by Mallory's phosphotungstic acid hema-

toylvlin stain which demonstrates small, flat spindle cells with scant, pinkish-brown-staining cytoplasm extending into a few protoplasmic end processes. The cells appear to be surrounded by a darker staining, yellowish-brown, fibrillar network. Between the coils there is still darker staining, orange-brown collagen. Of two lymph nodes examined, one shows evidence of metastases of the above described neoplasm. *Pathologic Diagnosis* Neurogenic sarcoma arising in a neurolemmoma.

Case 18—N. L., white, female, age 50, a housewife, was first seen, December 17, 1925, at which time she complained of severe headaches and difficulty in swallowing. Examination showed deafness in the right ear and a moderate degree of bilateral nystagmus. The blood pressure was 148/102. Rectal examination revealed a large nodular tumor mass in the anterior rectal wall 2 cm from the anal margin. Its upper limit was well above the reach of the examining finger. Adjacent tissues were infiltrated. Proctoscopic examination showed a nodular mass not involving the mucosa. A biopsy was taken from this rectal mass. The urine contained a trace of albumin and many leukocytes per low power field. A neurologic consultant believed the findings to be due to metastases at the base of the skull. No form of surgical therapy seemed indicated and, accordingly, she was discharged, December 23, 1925. Her physician reported that she died at home shortly after her return. Death occurred from exsanguination following several massive hemorrhages from the rectum.

Pathologic Examination—Microscopic A neoplasm composed of whorls and interlacing cords of spindle cells. Parts of the neoplasm are reticular in character, giving the appearance of Antoni's Type B tissue. *Pathologic Diagnosis* Neurogenic spindle cell sarcoma.

Summary of Treatment and End-Results—Table VII summarizes the treatment carried out in the 18 cases. As will be noted, radical surgical

TABLE VII
SUMMARY

Location	Type	No of Cases	Treatment	
Stomach	Neurolemmoma	4	{ Partial gastric resection	1
			{ Total gastrectomy	1
			{ 2 cases incidental to carcinoma of the stomach	2
	Neurogenic sarcoma	3	{ Partial gastric resection	1
			{ Simple excision	1
			{ Biopsy	1
Intestine	Neurofibroma	3	{ Resection segment of small intestine	1
			{ None (autopsy findings)	2
Mesenteries	Neurolemmoma	1	{ Partial gastric resection obstructive resection of transverse colon	1
	Neurogenic sarcoma	1	{ Resection of 2 segments of small intestine and mesentery	1
Retroperitoneal	Neurolemmoma	1	{ Excision (complete)	1
	Ganglionated neurofibroma	1	{ Excision (? complete)	1
	Neurogenic sarcoma	4	{ Excision (partial)	1
			{ Excision (complete)	1
			{ Biopsy	2
Total		18		18

removal was undertaken in ten instances, with two hospital deaths. One of these occurred following resection of a segment of small intestine for a neurofibroma which had caused chronic intussusception, while the other followed the removal of a neurogenic sarcoma situated in the mesentery of the ileum. Of the patients operated upon for gastric lesions, one is entirely well, four years following subtotal gastrectomy for a neurolemmoma, and one, two years following total gastrectomy for a similar neoplasm. The one patient upon whom subtotal gastrectomy was performed for a neurogenic sarcoma was operated upon too recently for the follow-up history to be of significance.

The male patient found to have the large neurolemmoma of the gastrocolic ligament which required partial gastrectomy as well as resection of a portion of the transverse colon for its complete removal, was well one year later. Since that time it has been impossible to trace this case.

Complete or partial removal was carried out in four of the retroperitoneal tumors. The one case of neurolemmoma in which complete removal was possible has been followed for only eight months. During this time no evidence of recurrence has been noted. Another patient, having had what was thought to be a complete removal of a neurogenic sarcoma, has been followed for four years and seven months and is entirely well and free from recurrence. The patient who proved to have a retroperitoneal cystic neurogenic sarcoma which involved the small intestine secondarily, died two years following operation, presumably of recurrence. In this case it was realized at the time of the celiotomy that removal had not been complete.

The six-year-old girl who presented the retroperitoneal ganglionated neurofibroma, which was incompletely removed, has remained well for ten years.

CONCLUSIONS

Since the nerve sheath tumors which are encountered within the abdominal cavity are chiefly of local malignancy, the prognosis following surgical removal is relatively good. Due to the odd or unusual situations in which they are apt to be found, operations of considerable magnitude are often necessary in order to insure complete removal. The end-results would seem to justify such operative procedures, wherever they are feasible.

BIBLIOGRAPHY

- ¹ Harrison, R. G. Further Experiments on the Development of Peripheral Nerves. *Am Jour Anat*, 5, 121, 1906.
- ² *Idem*. Neuroblast Versus Sheath Cell in the Development of Peripheral Nerves. *Jour Comp Neurol*, 37, 123, 1924-1925.
- ³ Verocay, J. Zur Kenntnis der Neurofibrome. *Beitr z path Anat u z allg Path*, 48, 1, 1910.
- ⁴ Masson, P. Experimental and Spontaneous Schwannomas (Peripheral Gliomas). *Am Jour Path*, 8, 367, July, 1932.
- ⁵ Antoni, N. R. E. Über Rückenmarkstumoren und Neurofibrome, *Studies zur pathologischen Anatomie und Embryogenese, mit einem klinischen Anknüpfungspunkt*. Munch, J. F. Bergmann, 1920.

- ⁶ Mallory, F B Type of Cell of the So-Called Dural Endothelioma Jour Med Res, 4, 349, March, 1920
- ⁷ Penfield, W Encapsulated Tumors of Nervous System, Meningeal Fibroblastomata, Perineurial Fibroblastomata and Neurofibromata of von Recklinghausen Surg, Gynec and Obstet, 45, August, 1927
- ⁸ *Idem* Tumors of the Sheaths of the Nervous System in Cytology and Cellular Pathology of the Nervous System New York, Paul Hoeber, Inc, 3, 955, 1932
- ⁹ Penfield, W, and Young, A W The Nature of von Recklinghausen's Disease and the Tumors Associated with It Arch Neurol and Psychiat, 23, 320, February, 1930
- ¹⁰ Stout, A P The Peripheral Manifestations of the Specific Nerve Sheath Tumor (Neurolemmoma) Am Jour Cancer, 24, 751, August, 1935
- ¹¹ *Idem* The Malignant Tumors of the Peripheral Nerves Am Jour Cancer, 25, 1, September, 1935
- ¹² Geschickter, C F Tumors of the Peripheral Nerves Am Jour Cancer, 25, 377, October, 1935
- ¹³ Stewart, F W, and Copeland, M M Neurogenic Sarcoma Am Jour Cancer, 15, 1235, July, 1931
- ¹⁴ Hosoi, K Multiple Neurofibromatosis (von Recklinghausen's Disease) Arch Surg, 22, 258, February, 1931
- ¹⁵ Harrington, S W Surgical Treatment in Fourteen Cases of Mediastinal or Intra-thoracic Perineurial Fibroblastoma Jour Thor Surg, 3, 590, August, 1934
- ¹⁶ Eusterman, G B, and Senty, E G Benign Tumors of the Stomach Surg, Gynec and Obstet, 34, 5, January, 1922
- ¹⁷ Elhason, E L, and Wright, V W M Benign Tumors of the Stomach Surg, Gynec and Obstet, 41, 461, October, 1925
- ¹⁸ Balfour, D C, and Henderson, E F Benign Tumors of the Stomach ANNALS OF SURGERY, 85, 354, March, 1927
- ¹⁹ Geschickter, C F Tumors of the Digestive Tract Am Jour Cancer, 25, 130, September, 1935
- ²⁰ Minnes, J F, and Geschickter, C F Benign Tumors of the Stomach Am Jour Cancer, 28, 136, September, 1936
- ²¹ Cabot Case No 21112 Spindle Cell Sarcoma of the Stomach, Probable Neurofibrosarcoma New England Jour Med, 212, 485, March 14, 1935
- ²² Cabot Case No 23312 Neurogenic Fibrosarcoma of the Stomach New England Jour Med, 217, 226, August 5, 1937
- ²³ Raiford, T S Tumors of the Small Intestine Arch Surg, 25, 122, July, 1932
- ²⁴ Rankin, F W, and Newell, C E Benign Tumors of the Small Intestine Surg, Gynec and Obstet, 57, 501, October, 1933
- ²⁵ Goldberg, S A Unusual Neoplasms of the Small Intestines Am Jour Clin Path, 9, 516, July, 1939
- ²⁶ Cohn, S, Landy, J A, and Richter, M Tumors of the Small Intestine Arch Surg, 39, 647, October, 1939
- ²⁷ Cabot Case No 24011 Neurogenic Fibrosarcoma of the Ileum New England Jour Med, 218, 39, January 6, 1938
- ²⁸ Klingenstein, P Benign Neoplasms of the Small Intestine Complicated by Severe Hemorrhage Report of 2 Cases, Operative Intervention and Recovery Jour Med Sinai Hosp, 4, 972, March, April, 1938
- ²⁹ Miller, A J, and Frank, L W Neurofibrosarcoma of the Small Bowel ANNALS OF SURGERY, 109, 246, February, 1939
- ³⁰ Keith, A R A Case of Neurofibroma of the Rectal Wall Trans Am Proct Soc, 38, 68, 1937
- ³¹ Woolf, M S Neurofibroma of the Rectum California and West Med, 49, 463, December, 1938

- ³² Glenn, F Neurogenic Fibroma of the Transverse Colon Surgery, 6, 703, October, 1936
- ³³ McDonnell, C H Neurofibromatosis of Bladder and Prostate Am Jour Surg, 34, 90, October, 1936
- ³⁴ Rankin, F W, and Major, S G Tumor of the Mesentery Surg, Gynec and Obstet, 54, 809, May, 1932
- ³⁵ Warren, S, and Sommer, G N J, Jr Fibrosarcoma of the Soft Parts with Special Reference to Recurrence and Metastasis Arch Surg, 33, 425, September, 1936
- ³⁶ Schrager, V L Surgical Aspects of Neurogenic Tumors of the Abdomen Surg, Gynec and Obstet, 68, 1085, June, 1939
- ³⁷ Trout, H H, and Meekins, G E Retroperitoneal Sarcoma Surg, Gynec and Obstet, 31, 622, December, 1920
- ³⁸ Hansmann, G H, and Budd, J W Massive Unattached Retroperitoneal Tumors J A M A, 98, 6, January 2, 1932
- ³⁹ Judd, E S, and Larson, M Retroperitoneal Tumors Surg Clin North Amer, 13, 823, August, 1933
- ⁴⁰ Frank, R T Primary Retroperitoneal Tumors Report of Three Cases and 107 Cases from the Literature Surgery, 4, 562, October, 1938
- ⁴¹ Andrus, W DeW Tumors of the Chest Derived from Elements of the Nervous System Jour Thor Surg, 6, 381, April, 1937

DISCUSSION—DR FREDERICK A COLLIER (Ann Arbor, Mich) It is obvious that the two types of tumors that have been presented to us in the last two papers are surgical rarities. However, I think they are not so uncommon but that any of us may encounter them at any time. There is very little for me to add, but I should like to emphasize the close clinical relationship between these tumors. They may present a clinical entity and, if such be the case, I think that both types of tumors might well be included in it. It is very difficult, often impossible, for the surgeon who is operating upon one of these tumors to tell whether it is a leiomyoma or whether it is a neurogenic tumor, and I doubt whether anyone can draw the distinction between the two at the time of operation. It is likewise rather difficult for the pathologist to make this distinction.

When Doctor Lahey asked me to discuss his paper, I looked up our cases of leiomyomas and I found three. We then subjected these three cases to stain designed to bring out the changes found in the neurologic tumors. We found that only two of them actually were leiomyomas, while one was a neurogenic tumor, which has been presented in Doctor Ransom's paper.

I wish to present one case of a tumor of the stomach of the neurolipoma type that can be contrasted with the cases of leiomyoma presented by Doctor Lahey to show that these two pathologic entities present similar clinical and gross pathologic pictures. The roentgenogram and photograph of it are shown under Case 3 in Doctor Ransom's paper. The patient an obese male, age 51, gave a vague history of indigestion over the past two years. Six months before he came to the hospital, he had a violent hemorrhage, vomiting blood in large amounts. This happened again one month before we saw him. When he arrived in the hospital, his hemoglobin was 28 per cent, but his nutrition was excellent.

The roentgenologic examination was a little puzzling, although the presence of a rather large tumor in the stomach was clear. The gastric acids were within normal ranges. The roentgenographic appearance was highly suggestive of carcinoma but the other factors were somewhat against this diagnosis. He was operated upon and the tumor removed, which, as can be seen, presents a picture that is indistinguishable from some shown by Doctor

Lahey It proved to be a neurolemmoma. The ulcerations in the mucosa are apparently rather typical of both the leiomyomas and the neurolemmomas. When the tumor was palpated before its removal, it was so freely movable that it gave the sensation of being entirely intragastric. There were excavations in the tumor just beneath the opening in the gastric mucosa, but it was impossible to decide whether the bleeding had come from vessels in the tumor or in the gastric wall.

I believe we must regard these two tumor types as giving similar clinical pictures. If a patient gives a history of severe hemorrhage, has normal gastric acidity, and has a tumor demonstrable roentgenographically, one should think of the possibility of one of these tumors being present. They both have benign and malignant phases and operation should be advised for them. I would like to ask Doctor Lahey whether the tumors in his series were examined by special stains designed to bring out neurofibers. It would be interesting to do this if it has not been done, since some of them might well be neurolemmomas.

DR JOHN J. MORTON (Rochester, N. Y.) These tumors of neurogenic origin are quite interesting. We have had several of them, I do not know quite how many, and I did not have an opportunity to look them up before I came away. Sometimes when they are in the retroperitoneal position they are very difficult tumors to remove. They are organ-displacing, often very large, and they mold themselves against the spine so that you have no opportunity to develop an edge. They are relatively inelastic and hard to roll over. We operated upon a woman who illustrated how large they may become. Roentgenographically, the mass indented the greater curvature of the stomach, pushed the kidney against the diaphragm, pushed the descending colon toward the midline and flattened out the splenic flexure. It had been slowly increasing in size during the previous six years.

Operation disclosed enormous vessels going into the tumor, and her condition became so bad that we were obliged to stop. Her blood pressure went to where it could not be recorded and we abandoned the operation. After a ten-day delay, I went in again and removed it. The tumor originated in one of the nerve sheaths and was benign. She is well now, seven years since operation.

Only last week, I had another tumor involving the terminal ileum, very similar to one of Doctor Ransom's, which proved to be a neurogenic sarcoma. This tumor occurred in a man, age 55, who gave a history of incomplete intestinal obstruction for over a year. He had complete studies by G. I. series, without finding any evidence of the tumor. But there was persistent blood in the stools and, finally, a movable tumor was demonstrated. Sometimes it could be felt in the abdomen, at other times it would disappear, and then, later on, could be felt in the pelvis. This involved the terminal ileum and it had definite nerve sheaths running to the tumor. There were some evidences of metastases in the nodes leading away from it. Microscopically, it was a fibrosarcoma, which brings me to another point, namely, that these fibrosarcomas are usually locally invasive. They tend to recur locally and to remain local for a long time. I think that we should try to get them out whenever we can because we have an opportunity to really cure these patients.

I recall another patient who was operated upon elsewhere three years before I saw him, with a diagnosis of neurogenic sarcoma involving the lower end of the left ureter. When he was sent to me, this tumor had recurred and it was so enormous it practically involved the whole pelvis. I told the doctor that if it were a neurogenic sarcoma, which I verified from the other hospital,

I did not think it would be radiosensitive and that it was inoperable as far as I could see. He said, "Doctor, you cannot let him down like that. You have got to do something." So I said, "Well, we will irradiate him but it won't do any good." To my surprise the tumor went down from a very large-sized tumor to one about the size of a grapefruit. At that point, he could stand no more radiation. His blood count was in the neighborhood of 2,000 white cells and we could not get it to come up.

It was then decided that we might perhaps be able to get it out. So we catheterized the ureter, and I went in and after fighting through a lot of adhesions, finally got down to the tumor, which was quite well encapsulated. I removed it in pieces. It was a neurogenic sarcoma. Six months later, the man complained of pain around his spine, which was, I thought, of a sort of girdle type, but it occurred to me that it was not correct for this type of tumor. He had also a little jaundice. So we subjected him to a cholecystogram and found he had gallstones. That gave me another opportunity to go into his abdomen, which I did, removing his gallbladder and, incidentally, took the opportunity to examine the site of the operation. It was absolutely free of recurrence of the tumor, and that was two years ago. He was in the office last week and he had no signs whatever of recurrence.

DR J. SHELTON HORSLEY (Richmond, Va.) I wish to report two cases of leiomyosarcoma of the stomach and a case of neurofibroma of the mesocolon. It is possible that they may be very cellular myomatas but the number of active cells in many of the sections and the mitotic figures would seem to indicate a low-grade leiomyosarcoma in the tumors of the stomach.

Case 1—W. T. C., white, female, age 62, married, was admitted to the hospital, August 6, 1937. For several days she had been bothered with a cough and a feeling of tightness in her chest. She had been gradually losing appetite and weight for the past six months. There was no history of bleeding from the stomach or bowel, and no nausea or vomiting or any unusual gastric complaint. Her weight upon admission was 115 pounds. There was a mass in the upper left abdomen involving the stomach. There was a large quantity of fluid in the right pleural cavity, from which 800 cc of clear yellow fluid was aspirated.

Operations—Five days after admission she was operated upon under local anesthesia, and a large tumor was found which involved much of the lesser curvature of the stomach. The liver seemed normal. The pyloric end of the stomach was not involved, and a mid-gastric or "sleeve" resection was performed, though this type of operation does not usually give good functional results. Recovery was satisfactory except that the stomach did not empty well for several weeks. The pleurisy cleared up after a few aspirations. The patient was seen about two weeks ago and was apparently free from any recurrence.

Pathologic Examination—*Gross* The specimen consists of the midportion of the stomach and the attached tumor, involving much of the lesser curvature of the stomach. It is bosselated, and the protrusions are smooth. Some portions are yellow and others are darker in color. The tumor measures 14×9×7 cm. The segment of the stomach removed measures 12 cm along the lesser curvature and 18 cm along the greater curvature. The cardiac end is smaller than the distal end. The mucosa seems to be about normal, though there are a few punctate erosions along the lesser curvature. The mucosa moves smoothly over the wall of the stomach. On section the tumor is solid but is soft with various nodules on the cut surface. They seem to consist of soft granular tissue divided into lobules. The tumor apparently sprang from the muscular coat of the stomach along the lesser curvature.

There is no history to indicate how long the growth had been present, though the patient is a very intelligent woman, and it is probable that it was not palpable very long before she noticed it.

Histologic Examination shows small spindle-shaped cells that are fairly active. There are mitotic figures. From the apparently rapid growth and the activity of the cells it appears to be doubtless malignant, probably a Grade I leiomyosarcoma.

Meigs (Meigs, Joe Vincent. Fibroma of the Ovary with Ascites and Hydrothorax. *ANNALS OF SURGERY*, 110, 731, October, 1939) and others have called attention to the association of hydrothorax with fibroma of the ovary. It may be that in this instance there was an association of hydrothorax with the tumor of the stomach.

Case 2—A. P. B., white, female, age 48, had, for several years, noticed a mass in the abdomen. It had only recently become tender. On admission to the hospital, August 7, 1938, it appeared to be about the size of a large grapefruit. The patient had had six children, the youngest being ten years old, there had been two miscarriages. An ovarian cyst had been removed a good many years ago. The tumor was slightly movable and rather soft. Roentgenologic examination of the gastro-intestinal tract was negative except for showing pressure deformity of the greater curvature of the stomach. It was thought that there was a mass in the abdomen which also displaced the colon.

Operation—August 12, 1938. Under ethylene anesthesia. There was a considerable amount of clear fluid in the abdominal cavity. The tumor sprang from the posterior wall of the stomach by a broad pedicle. It was easily removed. The mucosa of the stomach was not involved. The patient made a satisfactory recovery.

Pathologic Examination—Gross. The tumor measures 15x11.5x12 cm. It is oval in shape and of irregular contour. Part of it appears to be soft, as though it contained fluid. The pedicle was from the stomach and contained a section of all of the wall of the stomach except the mucosa. On section there is a necrotic area with some hemorrhagic exudate, but most of the cut surface is divided into lobules and lobes, as a myoma. There is an area in which there appears to be degeneration, and the tissue is soft and loose, being apparently attached only at one margin.

Histologically, the tumor shows spindle-shaped cells with smooth muscle, they are quite active, with a few mitotic figures present. In some areas there is degeneration, probably from interference with the circulation.

Speaking of leiomyosarcoma of the stomach, Ewing says (Ewing, James. *Neoplastic Diseases*, 3rd ed., 278, W. B. Saunders Co., Philadelphia) "The structure varies between considerable limits. In some cases the type approaches that of a cellular myoma, and the recognition of a myogenous origin is readily accomplished. Or the cells are of large spindle form, and the designation as a myosarcoma depends on the attitude of the observer."

The following is a case of neurofibroma.

Case Report—K. W., white, female, age 39, had been having tarry stools for many weeks. She had vomited off and on when she was on a milk diet, but did not vomit blood. She was anemic, her hemoglobin was 42 per cent, red cell count 2,560,000, and white cells 4,200.

The physical examination was essentially negative except for a scar in the lower right abdomen where the appendix had been removed a good many years ago. Roentgenologic examination was negative. She had not vomited during the two weeks before admission. She suffered no pain, but had been weak and anemic for four or five years and recently this condition had increased. The tentative diagnosis was duodenal ulcer.

Operation—February 20, 1928. The stomach and duodenum appeared normal. In the hepatic flexure of the transverse colon was a flat mass arising from the transverse mesocolon and attached to the jejunum. It was extremely vascular. A part of the jejunum and a segment of the transverse colon were resected. The tumor proved to be a degenerating neurofibroma arising from the transverse mesocolon and invading the

upper jejunum at one point. It was at this point in the jejunum from which the hemorrhage occurred.

The patient made a satisfactory recovery, and when heard from recently was quite well.

Histologic examination showed an unusual type of tumor. Dr. A. C. Broders, of the Mayo Clinic, reported, March 5, 1928, as follows: "I am of the opinion that this tumor is a degenerating neurofibroma. I have never seen one in this region, but it has a microscopic picture characteristic of those found elsewhere."

DR. FRANK H. LAHEY (Boston, Mass., in closing): It is interesting that these two types of benign gastric lesions could be discussed here. It is valuable to call attention to these groups. I neglected, or did not have time, to state there had been no recurrence in the follow-up, and this is a very hopeful type of case.

Doctor Cave suggested that I should say just a word about something of the anesthetic management of the gastrectomies and total gastrectomies because it involves differences of opinion. It also brings up a point which I think we should all have in mind, and that is the use of spinal anesthesia. Now, I do not want to debate that question because I know how very controversial it is, but certainly it has made the operation very much easier for us. Because we have had the opportunity in a limited number of cases, now about 31 or 32, to employ this new type of continuous spinal anesthesia advocated by Doctor Lemmon of Philadelphia, I would like to speak about it.

When this method first was suggested to us by Doctor Lemmon, I had a considerable prejudice against it and I think it is but fair to state that that was my position. I felt that permitting an indwelling needle to remain within the spinal canal during an operation was undesirable. I feel that to repeatedly introduce anesthetic solution into the spinal canal during an operation was also unsatisfactory. It is but fair to say, however, that after sending an anesthetist to Philadelphia to learn the method, its employment, in even a limited number of cases, has been entirely satisfactory. I would certainly suggest in the light of our experience up to the present that you do not make the mistake that I made in my prejudice against it. If it continues to give the results that our experience and Doctor Lemmon's up to the present promises, it fulfills many of the requirements for spinal anesthesia that are so desired. It permits the introduction of a small dose, the production of a short anesthesia which can be added to as is required and prolonged with repeated doses up to any extent. There have been no neurologic complications. In the past, one of the most undesirable features of spinal anesthesia over long periods of time has been the large amount of anesthetic agent which had to be introduced so that the length of anesthesia was established no matter what fraction of it was used.

DR. HENRY K. RANSOM (Ann Arbor, Mich., closing): I am glad that this paper on a rather unusual subject has stimulated such an interesting discussion. The two types of tumor under consideration, i.e., those arising from nerve sheaths and those arising from smooth muscle, are in fact very similar, and often distinguished from one another only by special studies and even then at times with considerable difficulty. This distinction between the benign nerve sheath tumors and the leiomyomas, as well as their malignant counterparts, is largely one of academic interest, since from the standpoint of symptomatology, roentgenologic findings, and surgical treatment, they are the same. Since the prognosis is relatively good, an effort should be made to recognize such tumors at an early date, and even though radical operations are required for their removal, the results justify such procedures.

ILEOSTOMY*

HENRY W. CAVE, M.D.,

AND

WILLIAM F. NICKEL, JR., M.D.

NEW YORK, N. Y.

DURING the past decade considerable interest has been aroused in the surgical treatment of ulcerative colitis. Ileostomy, as the first stage in the removal of the colon as well as a complete method in itself to effect "cure," merits discussion. Appendicostomy, cecostomy and, except for certain cases, colostomy have been discarded as ineffectual surgical measures, and have in the past and do at present complicate further surgery when undertaken. Ileostomy deserves no such fate.

Realizing the magnitude of subtotal colectomy with subsequent removal of the rectum, the question has repeatedly been asked, Will ileostomy alone cure this disease? There are those^{1 2 3} who have felt if ileostomy is performed early enough in the course of the disease no further operative interference is needed and the ileostomy can be closed when the process has healed. Others^{4 5 6 7} are of the opinion that ileostomy alone is seldom curative and, except in rare instances, should remain permanent.

This presentation will submit data concerning the indications for ileostomy—the preoperative medical preparation, the immediate preoperative surgical preparation, the technic of ileostomy, the postoperative management as to diet, the care of ileostomy, and the complications and the mortality. Also, the results of a questionnaire sent to members of three national surgical associations⁸ will be given, as well as experiences with ileostomy at the Roosevelt Hospital, New York.

At the outset, it is well to emphasize the importance of complete medical control of both preoperative and postoperative periods, and throughout the illness of these patients. Let the physician and surgeon jointly decide the time for surgical intervention and, further, the follow-up should be carefully observed by both physician and surgeon.

Indications for Ileostomy—To subject an individual to ileostomy which, in all but a small percentage, is permanent requires cautious reflection. In the small group of about 10 per cent, where the rectum is free of the disease, ileosigmoidostomy is eminently suited, and in an equally small group, where the disease is proven limited to the left colon, colostomy, relatively easily managed, suffices.

The conditions requiring ileostomy may be classified under two headings: (1) Emergency, (2) elective.

Emergency—In the emergency group impending perforation often necessitates immediate intervention. Heretofore, massive hemorrhage has been

* Read before the American Surgical Association, St. Louis, Mo., May 1, 2, 3, 1940.

considered an indication for emergency ileostomy. Realizing by past experiences that ileostomy, performed at or immediately following massive hemorrhage, is almost always fatal, and that vitamins K and C have been a competent factor in controlling bleeding, we discard this from the lists of indications.

Elective—More numerous are the patients in whom elective surgery can be planned. A previous report from the Gray Service of the Roosevelt Hospital⁹ pointed out that the medical prognosis in the individual case depends upon the extent of irreparable damage to the colon and the identification and control of factors contributing to activity of the disease.

In certain instances despite advanced and permanent organic changes in the colon, evaluation and control of these factors permits the individual to remain largely, if not completely, symptom free under ordinary conditions of life or activity. Such individuals necessarily must be classed as instances of satisfactory response to medical care. Surgical intervention is not indicated.

Others, despite repeated investigation and reevaluation, present progressive extension of the pathologic changes and are continuously handicapped by chronic symptoms of greater or lesser severity. Still another group continues to exhibit the characteristic periods of activity and remissions, accompanied by an extending involvement of the colon, and are seriously handicapped by their disease. Surgery must be considered for these two groups.

The results of elective surgery will depend upon two basic factors: (1) Technical procedures, (2) the preoperative and postoperative care. This implies and actually necessitates continuous cooperation by the surgeon and the internist.

Preoperative Medical Study and Preparation—Adequate preparation for surgery demands meticulous, detailed, and prolonged medical investigation of the patient, in some instances as long as one year. Many abnormal conditions which should be corrected among them are: (1) Active food allergy; (2) Disturbed physiology of other parts of the digestive tract (gastric acidity produces diarrhea and flatulence, hypomotility of the colon with right-sided retention contributes to the degree of pain); (3) Psychic and emotional factors; (4) Conventional diets too low in proteins, thiamine chloride, vitamins A, C, D, and certain members of the B complex; (5) Anemias—hypochromatic and microcytic, at times hyperchromatic and macrocytic; (6) Disturbances of mineral metabolism involving particularly calcium, phosphorus and sodium chloride; (7) General malnutrition and inanition.

Anesthesia—We have, in over one-half of the cases, used avertin, gas, oxygen and ether. Lately, however, we have used novocain, procaine hydrochloride and pontocaine, in small amounts, administered low in the canal, as a prolonged anesthesia is not necessary in carrying out this procedure.

Immediate Preoperative Surgical Preparation—Immediate preoperative surgical preparation consists, principally, in thoroughly cleansing the colon by the use of daily irrigations with warm saline solution. It is important

that the fluid balance and the blood chemistry be regulated by the administration of infusions and, if necessary, transfusions. Recently, it has been shown that before and after surgical procedures, the vitamins, especially vitamin C, are markedly reduced, therefore, vitamin supplements are administered sufficiently to saturate the patient.

A nonresidue diet is advisable for 36 hours prior to proposed operation, and lead and opium pills and paregoric render the bowel quiescent.

Technic of Ileostomy—Ileostomy as a surgical procedure has been known for 150 years¹⁰. It was not, however, until 1913 that John Young Brown¹¹ made use of this procedure in ulcerative colitis. Since then various modifications of the Brown ileostomy have been employed. One of us (H. W. C.) for the past two years, has employed a form of ileostomy which has proved satisfactory.

A modified McBurney incision is made well away from the anterior superior spine (Fig. 1). The peritoneum is opened. The terminal ileum is carefully inspected (in about 25 per cent of the cases it was found that the terminal ileum appeared reddened, edematous and rigid, yet when reexamined at the stage of subtotal colectomy, only in four instances was it actually involved). We lay great stress about the advisability of not exploring the surrounding peritoneal cavity, at this time, for the reason that disaster has come of this. The wall of the cecum is thinned out. In places it is diseased and it is easy to perforate the cecal wall with the examining finger if great care is not taken. Garlock¹² cites one experience when, inadvertently, he pushed his examining finger through the diseased wall of the cecum.

The exact site of division of the ileum depends upon the amount of inflammatory process which is found to be present, and upon previous roentgenologic studies. Usually six to eight inches from the ileocecal valve, the small bowel will be found to be normal. Two fascades of vessels in the mesentery are then divided for about three inches. It is, at this point, judicious to see that the ileocolic artery has not been injured. A small stab wound is then made one and one-half inches below the umbilicus, just to the left of the midline. This is to be the site of the distal divided end of the ileum, which becomes a mucous fistula. One purpose of placing this mucous fistula at this point is that at the second stage, when the entire colon is removed, this mucous fistula is in the line of the long, left, paramedian incision. Certainly, the most difficult part of subtotal colectomy is the division of the splenophrenic-colic ligament and it is for this reason that a long incision on the left side of the abdomen is preferable, so that this step of cutting the splenophrenic-colic ligament is made easier.

An Ochsner clamp is introduced through the stab wound below the umbilicus on the left side and is placed to the distal side, where division of the ileum is to be made. A Kocher clamp is introduced through the McBurney incision and this grasps the proximal portion of the ileum. The ileum is then divided transversely with the cautery or a carbolyzed knife (Fig. 2). The distal end of the divided ileum is then drawn out as a mucous fistula.

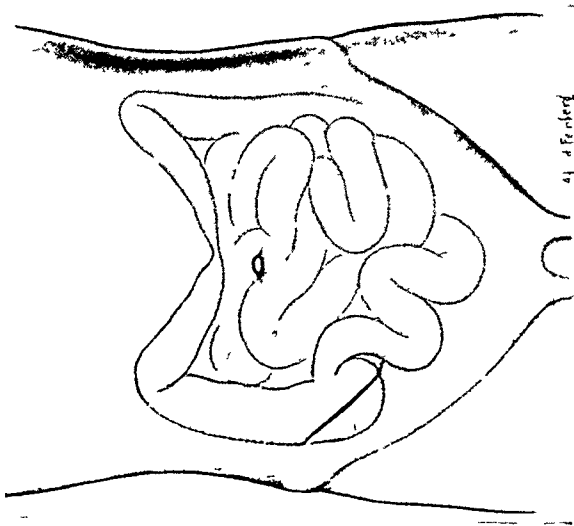


FIG 1—Diagrammatically representing a permanent structure in the transverse colon. The incision the lower angle curved well to the left. The entire incision should be well away from the anterior superior spine to permit the comfortable use of a bag.

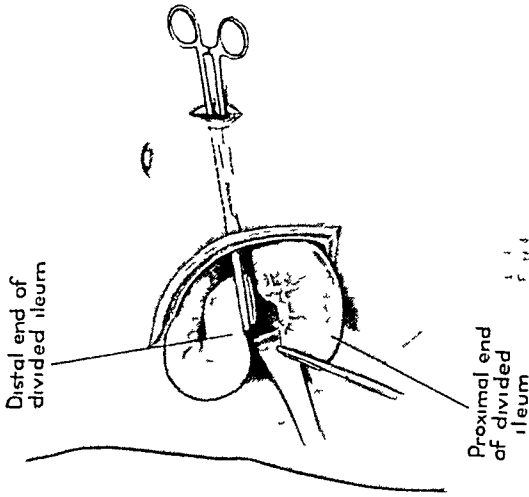


FIG 2—Distal divided end of ileum to be drawn through stab wound to left of midline. Proximal end brought out at lower angle of modified McBurney incision to constitute the permanent ileostomy opening.

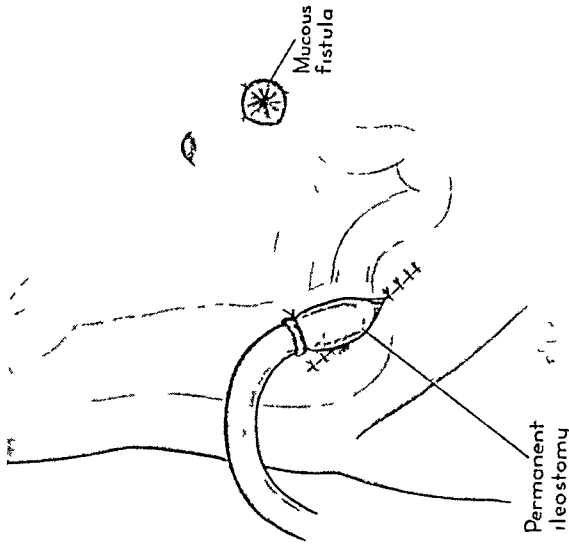


FIG 3—The permanent ileostomy with large caliber rubber tube in position. Also, showing a suitable site for the mucous fistula.

through the stab wound, to the left of the midline, and a few sutures are taken in the mesentery to prevent retraction (Fig 3)

The proximal end of the ileum is then brought out through the lower angle of the McBurney incision, in fact, of late, we have found it preferable to divide the fascia over the rectus muscle, push the rectus muscle medialward, if necessary divide its outer fibers, thus being assured that the ileostomy will be toward the midline and well away from the anterior superior spine. In order to prevent loops of small intestine from prolapsing through the rent in the mesentery, and also in an effort to prevent the ileostomy from prolapsing, interrupted sutures attach the cut end of the mesentery to the peritoneum well underneath, and to the fascia. The wound is now closed in layers about the protruding ileum (Fig 3)

Two inches of ileum should protrude from the anterior abdominal wall. The clamp is immediately removed from the protruding proximal ileum and a good-sized rubber tube is placed into the stoma and carefully tied with a segment of cotton tape. A greased gauze dressing is applied.

The tube connects with a bottle over the side of the bed and usually within 24 hours it begins to function. The tube usually remains secure in the ileum for about eight days, at which time it drops out and the contents of the ileum pour out on the anterior abdominal wall. Caution should be exercised to eliminate any excoriation of the skin.

We have found this best prevented by the use of *Fist*, applying compound tincture of benzoin, over this is sprinkled Fullers' earth, and a salve made of aluminum powder, cod liver oil and zinc oxide are frequently used. From the beginning, the patient is instructed to look after his own ileostomy. Pledgets of cotton are supplied to him in abundance so that the discharge may be wiped away at frequent intervals.

Postoperative Management—Immediately following ileostomy, a transfusion is administered. In order to insure the immediate functioning of the small bowel through the newly made ileostomy stoma, adequate fluids, by venoclysis, or Hartman's solution and 5 per cent glucose in saline are administered.

Serum protein, the chlorides and calcium content of the blood are carefully checked at intervals following operation. Determination of plasma and serum specific gravity is also of value in aiding the maintenance of chemical balance. If there is found to be a deficiency in vitamins K and C or if a raised prothrombin time is present, these vitamins are given. Thiamine chloride 25 mg is given intramuscularly for three days prior to operation and for the first ten days postoperatively. This vitamin assures an improved appetite and aids materially in coaxing these patients to begin eating early following the operation and maintains the desire for food. This factor is important in the restoration of function of the ileal stoma.

The day of the operation, the patient is urged to chew gum and is given cracked ice. For the first day postoperative, soda crackers and melba toast with cracked ice are alternated every two hours with orange or lemon juice.

until the ileostomy drainage begins. A soft, low residue diet is given in the afternoon as small feedings every three hours. The second day postoperative the soft diet is continued as six feedings with copious amounts of fluids. On the third day after operation, a more solid diet is permitted. This diet is continued until the tube drops out, usually from the eighth to the tenth day, when a regular diet is instituted, unless food idiosyncrasy is known to be present.

In those patients where the serum protein tends to be low in spite of transfusions, a high protein, high carbohydrate diet is advisable.

The following beneficial results are enumerated: (1) The ileal stoma functions usually within 24 hours. (2) There is a minimum amount of postoperative gas and distention, thus the risk of vomiting and ileus is minimized. (3) The sense of well-being is rapidly restored. (4) The weight is maintained, so that usually the convalescent weight loss is seldom more than three to five pounds.

Complications of Ileostomy—The complications of ileostomy, often annoying, are seldom fatal. Bleeding from the mucous membrane lining the stoma is occasionally thought by the patient to be involvement of the small bowel. In one instance bleeding so severe occurred that adrenalin and pressure bandages had to be resorted to.

Prolapse of the ileum is not uncommon in the earlier cases in our series before suture of the ileal mesentery to the fascia was carried out. Many prolapsed, several protruded four to six inches from the surface of the anterior abdominal wall, and still do. As yet, in no instance have we had to revise an ileostomy for this reason.

Retraction of the stoma from the abdominal wall may occur, especially in fat individuals where it has proved difficult to estimate the proper amount to withdraw from the abdomen. Careful fixation of the mesentery to the fascia will prevent this.

In three instances, narrowing of the stoma with impending stricture has resulted from too close suturing of fascia about the bowel. This we have overcome by repeated daily dilatations by the patient's index or little finger.

A poorly selected site for the ileal stoma in our one experience (too near the anterior superior spine) necessitated an additional operation in order to transplant the opening nearer the midline of the abdomen.

Due to an ill-advised suture in the ileal wall itself, secondary openings proximal to the stoma developed, in two of our patients, necessitating revisions in both instances.

Intestinal obstruction, particularly of loops of the small intestine, is a complication to be dreaded. One of the patients in our series suffered from acute ileus on two different occasions. Enterostomy fortunately relieved the first obstruction, removal of the ileostomy stoma to the left side of the abdomen was deemed necessary following the second episode, and subsequently proved to be justified. Two other individuals were temporarily blocked, were hospitalized and were relieved by palliative measures.

ILEOSTOMY

An unusually striking sequela of ileostomy was repeated attacks of pronounced collapse due to the loss of NaCl from the sudden and rapid ejection of fluid from the ileostomy stoma. This patient was so debilitated that he has returned to the hospital upon three occasions seeking intravenous administration of fluids and chlorides.

Results of Questionnaire—The answers to our questionnaire revealed noteworthy information. We were particularly interested to learn: First, if patients had been cured by ileostomy alone, and second, whether subsequent closure of ileostomy had been justified.

TABLE I
Ileostomy Without Closure

No. of Patients	
77	Results not given
26	Results given
	13 of these 26 were symptom-free, a few "cured"
	13 of these 26 symptoms continued
51	Deaths, or mortality of 33%
<hr/>	
Total	154

With the results given in only 26, excluding deaths, no conclusions can be drawn as the number is too small. It was of interest to note that in two patients the disease progressed beyond the ileostomy into the adjacent proximal loop, reemphasizing the now indisputable value of transverse or single barrel over loop ileostomy. However, the mortality following ileostomy of this group of 154 patients was 33 per cent, which is not unexpected considering the published reports of various other surgeons. This mortality impresses one with the seriousness of ileostomy. The principal reason for the mortality in many instances is that surgical aid is frequently sought too late. The acute, fulminating group with actual or impending perforation, massive hemorrhage, or chronic intractable patients who have been debilitated to a marked degree and who have been inadequately treated medically, are bad surgical risks. Admittedly, ileostomy is not a difficult technical procedure, it was, in the past, attended by a considerable mortality. Cattell's¹³ mortality of 22 per cent, Kunath's¹⁴ 83 per cent mortality following ileostomy in 12 patients, and our total mortality of 23 per cent, all emphasize the necessity of earlier surgical intervention and better preparation for operation. In certain individuals, thorough medical study and careful postoperative care are essential. In no small measure has the high mortality been due to a rapid and excessive loss of fluid and chlorides immediately after operation.

Of this small group who were subsequently closed, 59 per cent were restored to health, for an average of nine years. This is encouraging, yet from the answers it was difficult to conjecture the degree and the extent of the pathologic process prior to the preliminary ileostomy.

The shortest elapsed interval between establishment of ileostomy and closure was two months, the longest approximately seven years. The op-

imum time for closure (if they are to be closed) does not depend on the interval between the establishment of ileostomy and its closure, as on the condition of the bowel and extent of the colonic lesion as determined by roentgenologic and proctoscopic examinations and the clinical signs and symptoms

TABLE II

No of Patients	Ileostomy with Subsequent Closure
22 or 59%	Restored to health Follow-up 2-20 yrs (average 9 yrs)
9 or 25%	Recurred
	1—Nothing done
	3—Reoperated upon Second ileostomy necessary (2 of these symptom-free 1 not improved)
	5—Not stated what was done

Mortality in Those Closed

6 Deaths, or 16.7%

- 1 Died 1 mo later—leakage at site of anastomosis (ileosigmoidostomy)
- 1 Died 2 yrs later—recurrence
- 1 Died 8 yrs later—recurrence
- 3 Cause of death not stated

Nine of these patients showed a recurrence of their disease following closure, three were operated upon and second ileostomies were found to be necessary. It is our opinion that it is a rare experience to successfully close an ileostomy in ulcerative colitis when the colon shows extensive ulceration, fibrous or pseudopolypoid degeneration. Garlock,¹⁵ of the Mt Sinai Hospital, New York, is strongly in favor of preserving the rectum, in the hope that the process will subside to the point where it will be safe to close the ileal stoma and divert the fecal current through the anal opening by performing an ileoproctostomy. The mortality of 16.7 per cent, or even higher death rate, can be expected not only from technical risks but from late recurrence. Mackie's¹⁶ contention is endorsed, that "It is impossible to say that after any given period of freedom from activity the disease will not recur."

From replies received, but few of the patients fell into the acute, fulminating group, and it was evident that the majority of procedures carried out were of an elective nature.

EXPERIENCE WITH ILEOSTOMIES

FROM THE

GRAY SERVICE AT THE ROOSEVELT HOSPITAL

Three hundred five patients suffering from ulcerative colitis have been treated on the Gray Service at the Roosevelt Hospital during the last four years. Of these, 45 have been subjected to some surgical procedure. Sixty-nine maneuvers have been carried out on these 45 individuals. Of these, 30 have been ileostomies. There were 23 males and seven females. The

ILEOSTOMY

average age of these 30 patients was 29.8 years. The average duration of symptoms was seven years, the shortest illness recorded was two weeks and the longest was 25 years. It was of interest to note the status of these individuals when they came to surgery. Eight were subjected to operative interference on account of perforation, two on account of hemorrhage, three on account of obstruction and 17 because they were suffering from the disease in a chronic intractable form.

TABLE III
STATISTICAL SUMMARY OF ILEOSTOMY DEATHS

	No. of Cases	Deaths	Mortality
Ileostomies	30	7	23%
Emergency ileostomies	11	5	45%
Elective ileostomies	19	2	11%

Patient	Type	Cause of Death	Death
1 S B	Emergency	Inanition	
		Vitamin K deficiency	Medical
2 F G	Elective	Peritonitis	Surgical
3 F K	Emergency	Peritonitis	Surgical
4 G S	Emergency	Massive hemorrhage	Surgical
5 C D R	Emergency	Peritonitis	Surgical
6 J N	Emergency	Paralytic ileus	
		Hemorrhage	Surgical
7 W E	Elective	Embolism	Surgical
8 D R	Emergency	Peritonitis	Surgical

The extent of the pathologic lesion, as presented, showed Extensive ulceration in 17, fibrosis and shortening in 16, and pseudopolypoid degeneration in 12. In our experience with the earlier cases, we made a practice of suturing the distal divided end of the ileum and dropping it back in the peritoneal cavity. Realizing that a certain number of these cases would go for a long period of time before being subjected to subtotal colectomy, and due to a stricture with a subsequent blow out of a sutured distal end, it is brought out as a mucous fistula. One might well say that this was not necessary if careful roentgenologic study was made prior to ileostomy, in order to determine the presence or absence of an impending contracture. Cattell¹⁷ states "My decision not to drop back the ileum was based on the observation of marked contractures developed in the colon after ileostomy."

The most striking feature of our experience in this disease has been a rapid gain in the vast majority of these patients after ileostomy. The average weight gained in 16 of our 30 patients was 27 pounds. The average length of time in which the weight was gained was five and one-half months.

Of the total ileostomies, there were seven deaths, or a mortality of 23 per cent. In discussing the mortality statistics of our ileostomies, we have divided them into "emergency" and "elective" ileostomies. There were 11 emergency ileostomies with five deaths, or a 45 per cent mortality. Of the

elective ileostomies, there were 19, with two deaths, a mortality of 11 per cent. Of the two deaths in the elective group, one died of peritonitis due to embarrassment of the circulation of the bowel wall, a technical surgical error, the second succumbed of an embolus six days after operation. Of those in the emergency group that succumbed, three died of peritonitis and two died of hemorrhage. We are fearful of performing ileostomy upon patients in the presence of massive hemorrhages.

We did not assume that ileostomy alone or ileostomy with reestablishment of the fecal stream could have proven curative in any of the 30 patients reported from the Roosevelt Hospital Series, and was performed solely as a preliminary step to the radical removal of the diseased colon and rectum.

There is an amazing psychologic improvement in patients who have submitted to ileostomy, principally, we believe, because they realize some radical curative measure has been undertaken. Following this procedure, except for a short period postoperative, the patient gains in weight and in strength. The ileal stoma is occasionally relatively quiet at night, and although they suffer the annoyance of an artificial and misplaced anus, they finally and fully realize that in order to live they must put up with this inconvenience.

CONCLUSIONS

(1) Appendicostomy and cecostomy based upon false premises (irrigating the colon with antiseptic solutions, in the hope of destroying invading organisms and thus effecting a cure) are discarded as useless.

(2) Indications for surgery

A Impending perforation

B Progressive extension of pathologic lesion, patients continuously handicapped by the disease

C Patients exhibiting periods of activity and remissions destroying their usefulness

(3) Detailed and usually prolonged medical supervision should adjust the following disturbances

A Active food allergy

B Altered physiology of other parts of the digestive tract

C Psychic and emotional factors

D Avitaminosis

E Anemias

F Mineral metabolism involving particularly calcium, phosphorus and sodium chloride

G General malnutrition and inanition

(4) Prior to operation the fluid balance and blood chemistry are adjusted. Vitamin supplements are administered to maintain proper vitamin levels. A nonresidue diet diminishes the presence of small intestinal contents at the time of operation.

(5) A general and a small amount of spinal anesthesia are equally sufficient.

- (6) The steps of a new ileostomy are outlined
- (7) The feeding of dry foods, followed almost immediately by a regular diet, insures a minimal amount of gastric distention and forcible peristalsis, results in early functioning of the ileal stoma
- (8) The deductions from a questionnaire reveal that
 - A Ileostomy is rarely a curative procedure in ulcerative colitis
 - B In very rare instances, the continuity of the gastro-intestinal tract may be successfully reestablished
- (9) Ileostomy is, in the majority of instances, primarily carried out as the first step in the complete removal of the colon and rectum
- (10) At present, the mortality following ileostomy in the emergency group of our series was 45 per cent, however, in the elective group it was only 11 per cent

REFERENCES

- ¹ Stone, H B Penn Med Jour, 32-211, 1928-1929
Idem ANNALS OF SURGERY, 77, 293, 1923
- ² Strauss, A Surg Clin North Amer, 3, 1032, August, 1923
- ³ Trout, H H Virginia Med Monthly, 63, 1, April, 1936
- ⁴ Lahey, F H Surg Clin North Amer, 11, 245, 1931
- ⁵ McKittrick, L S, and Miller, R H ANNALS OF SURGERY, 102, 656, 1935
- ⁶ Crohn, B B, and Rosenok, B B Amer Jour Digest Dis and Nntrit, 2, 343, August, 1935
- ⁷ Rankin, F W ANNALS OF SURGERY, 107, 818, May, 1938
- ⁸ American Surgical Association
Southern Surgical Association
Western Surgical Association
- ⁹ Mackie, J J J A M A, 111, 2076, December 3, 1938
- ¹⁰ MacQuire, D P Amer Jour Surg, 29, 199, 1935
- ¹¹ Brown, J Y Surg, Gynec and Obstet, 16, 610, 1913
- ¹² Garlock, J H Personal communication
- ¹³ Cattell, R D Surg Clin North Amer, 19, 629-635, June, 1939
- ¹⁴ Kunath, C A Arch Surg, 32, 302-319, February, 1936
- ¹⁵ Garlock, J H Personal communication
- ¹⁶ Mackie, J M J A M A, 111, 2071, December 3, 1938
- ¹⁷ Cattell, R D Personal communication

DISCUSSION—DR HARVEY B STONE (Baltimore, Md) One may divide the cases upon whom ileostomy has been performed for the treatment of ulcerative colitis into three groups, dependent upon their subsequent course following ileostomy There is a small group that fail to improve either in their general condition or in the local disease in the bowel On the contrary, they get worse That group to which Doctor Cave has given a great deal of attention in his own work, although he did not emphasize it in the paper, probably are best treated by stage-colectomies A much larger group improve materially in their general condition They gain weight They gain strength Their blood count comes back to normal Their temperature returns to normal They regain their working efficiency but the disease in the bowel, although static, is not cured That is the group about which the late Dan Jones used to say that ileostomy cures the patient but it does not cure the disease, and of the total group of ileostomy cases, this group, I think, is by far the most numerous

Then there is a third smaller group who do recover, not only insofar as their general welfare is concerned, but the disease heals, consequent to the rest afforded the colon as a result of the ileostomy, and in these people the ileostomy may be closed and the alimentary tract restored to normal. I realize that there are many men, some of them quite experienced, who will deny the existence of such a group of cases—but there is such a group! It has been incontrovertibly proved by experience and, as a matter of fact, the statistics which Doctor Cave has just shown us reveal that in, I think, 37 cases of his total series closure was effected, and only 25 per cent of those closed had subsequent trouble. So that there is a group in which permanent definitive cure may be expected. It seems to me that the problem of the treatment of this disease should focus upon enlarging this group of cases at the expense of the other two groups, so that we may get more people in whom ileostomy can produce a definitive cure, and, to do this, it seems to me it is essential that the treatment be invoked before irreversible changes have taken place in the large bowel. I cannot see that there is much hope for a permanent cure after the disease process has extended into the wall of the bowel, under the mucosa, and converted the colon into a rigid, fibrous tube, therefore, I think that we should urge operation before these irreversible changes have taken place.

I believe there is at least a criterion which might be employed to decide when to advise ileostomy. In the past, I think it has been the custom to advise ileostomy on the basis of the two suggestions made by Doctor Cave. The progressively uninterrupted progress of the disease downward, what he calls his grave, continuous cases, or the intermittent but constantly recurrent group of cases. I would suggest that another test be applied in advising ileostomy, namely, the discovery, by repeated roentgenologic examination, of the beginning of permanent change in the large bowel. When the radiologist reports that all the haustration is disappearing from the colon and that, on fluoroscopic examination, it is beginning to lose its flexibility, you have there evidence of the initiation of irreversible changes, and that is the time to employ ileostomy before those changes have gone any further.

Why do we not do this? Well, I think there are two reasons. In the first place, clinically, many of these patients, even after having been ill a good while, enjoy a period, at least, of recovery, and the doctor and patient constantly hope that this individual case will, tomorrow or next week or some time soon, have a recovery which may be permanent, so that the constant hope of spontaneous or medical cure defers operation. I suggest that if roentgenologic examination shows changes in the organic structure of the colon, that hope be abandoned. The second reason ileostomy is deferred is because of the extremely disagreeable nature of the treatment. As a matter of fact, I think many people feel that the treatment is worse than the disease. It occurs to me that that is a challenge to surgery, to our technical mastery of this problem, to see whether there may not be some method by which a better type of ileostomy can be performed to diminish the disagreeable features consequent upon its performance.

(The speaker here demonstrated by lantern slides a procedure which he had employed in three cases.) After the ileostomy had been established, an incision was made mesially to it. A loop of ileum immediately above the stoma was drawn out, its two arms sewn together by a posterior suture, an incision made, similar to that of a Finney pyloroplasty between the two arms and the anterior suture completed. This resulted in the production of a loop that was self-anastomosed, and which formed a collecting reservoir immediately proximal to the position of the stoma.

This procedure was undertaken in the first instance to correct a very annoying, long prolapse through the ileostomy stoma. It did that efficiently, but it also considerably slowed up the number of discharges from the stoma, led to a considerable absorption of fluid and a thicker consistency of the material discharged. So that I have employed this procedure in two other cases, in the hope that this might improve the status of these people who have an ileostomy. This point in operative technic is merely offered as a first suggestion of an attack upon the problem of ileostomy, in order that it may be made a more tolerable condition and, therefore, reduce the reluctance of doctors and patients to subject patients to this form of treatment.

How can one tell when a patient, who has had an ileostomy performed, is a fit subject for closure of the stoma? Well, in addition to all the well-recognized tests, recovery from his illness, restoration to weight, blood count, *etc.*, in addition to a proctoscopic examination which shows a normal mucous membrane in the rectum and lower sigmoid and to roentgenologic study of the higher portions of the colon, I would suggest one further test. If a patient, otherwise apparently ready for closure of the stoma, has his colon injected per rectum with two liters of normal salt solution, the fluid retained a little while and then expelled, collected, centrifuged, and the precipitate examined microscopically for red cells and leukocytes, and none such found, I believe that one can then safely close the stoma.

DR FREDERIC W. BANCROFT (New York, N. Y.) I should like to discuss the third group that Doctor Stone referred to—the group where the ileostomy may possibly be closed. I have closed four. One caused a very sudden recrudescence of the disease, resulting in mortality. One, I followed for one year, and was well when last seen, one, for four years, who was still well. I should like to give an eight-year-old history in lantern slides, if I may, of a man whom I operated upon in 1932. (Doctor Bancroft here showed lantern slides of the condition of the man before operation, and then following his ileostomy in 1933.)

A barium enema study was made in 1934, at which time the patient was seen by Doctor Stone, who sigmoidoscoped him, and we thought we were safe in reimplanting the ileum. This operation was performed, in 1934, by transplanting the ileum into the transverse colon. He was well for about one year, and then had a recrudescence of his diarrhea after chopping wood, fishing and paddling a boat, so that, in 1935, the cecum and ascending colon were resected as far as the anastomosis. Since that time, he has been very well, has been able to carry on his business, and has been very active in fishing, hunting, climbing and golfing. Barium enemata, in 1936, 1937 and 1939, showed a moderate polypoid formation of the descending colon, which has decreased within the past year, and which shows, very definitely, the disappearance of the pipe-stem appearance of the bowel. It is my impression that this polypoid formation, in some cases, is the result of healing—and not the progress of the disease. It has been now three years since he has had blood in his stool. His only objection to me as a doctor is that I will not let him play 36 holes of golf a day. I have restricted this exercise, as he has a rather weak abdominal wall and I feel that golf may be too much of a thrust on his abdomen.

DR FRANK H. LAHEY (Boston, Mass.) I think this is an extremely important subject. I feel sure that a great many patients die needlessly every year due to the fact that we do not get the gastro-enterologists and the medical men to cooperate well enough with us about early ileostomies. Those of us who have the good fortune to have gastro-enterologists or medical men

associated with us, can get early ileostomies done because of the fact that we have made our mistakes together, and have learned not to put these cases off until the disease is too advanced. What we need is to get before the medical public the fact that this late delivery of patients with ulcerative colitis, who are candidates for ileostomy, to surgeons, results in most of the mortality of this disease.

We have had to date approximately 300 patients with ulcerative colitis, and it is only by the bitter experience with the results of delay that we have been able to convince even our own gastro-enterologists that these patients should be operated upon earlier. On the other hand, there are some things to be said in the gastro-enterologists' and medical men's favor who delay ileostomy. We must admit it is a very poor type of enterostomy and, no matter what one may say about its necessity, it must be admitted, also, that it is an undesirable type, therefore, no one wants it. It is but natural that the patient and his medical adviser should delay having it undertaken as long as they can. On the other hand, this is an extremely difficult psychologic situation and one, of course, that can and does result in undue delay and at times unnecessary fatalities.

I do not quite agree with Doctor Stone that this early change in the colon should be an indication for ileostomy because we have to admit that there are many patients with fairly rigid-appearing colons who are getting on very well. I wonder if I, myself, might not possibly accept a fairly rigid colon with some hazard rather than an ileostomy. From our experience with those patients who have had ileostomies (70 in number) in our hands and those patients who have not required surgery and who are getting on reasonably well without it (59 per cent of all the cases which we have seen), there are many who have quite rigid colons and who have had fairly rigid colons over a number of years but have still been able to manage without an ileostomy.

We should be careful as to the type of ileostomy which we employ. There is no doubt but that the end-ileostomy, of the divided type which has been described by Doctor Cattell in this clinic, is the best type. But this type requires considerable technical manipulation which in very advanced and toxic cases will undoubtedly result in fatalities which would not occur in less advanced types. It is, therefore, important to divide those cases into the very severely ill who will stand nothing more than the loop-ileostomy, even if it is undesirable, without manipulation of the colon in any way, and those in whom a divided-ileostomy may be performed and so implanted in the abdominal wall that later colectomy can be undertaken without difficulty.

One other point, and that is that everyone who deals with ileostomies will have trouble with them. We have had them prolapse and we have had them pull away, therefore, some time ago, we advocated the suture of the mesentery to the abdominal wall. This is a very important point in preventing prolapse and the pulling away of the ileum in these cases.

One other very important point is that some type of fairly tight suction tube be introduced into the ileostomy immediately after it is made until good wound healing has taken place, because liquid fecal discharge is one of the things that breaks the ileostomy down. Doctor Lium, an exsurgical fellow in our clinic, has devised a type of ileostomy tube which can be inserted into the ileostomy immediately, which will keep it dry while the wound heals soundly, and I think that is an important point.

We have here, I believe, a most difficult situation, and what Doctor Cave has said is extremely important—that is, we will always have difficulty as long as the gastro-enterologists or medical men handle these cases separately, and then turn them over to us as technicians solely to do these things. When they

can see and feel responsible for the undesirable effects of delay, and when even after temporary good results with ileostomy, later recurrence of blood, increased pulse rate and elevated temperature and fatalities also take place as the result of delay, then we will get them to submit their patients to early ileostomy and to early colectomy

One other thing, and that is you can assure a patient with ileostomy that after you have performed the colectomy the ileostomy will be easier to manage, the number of stools will be less, and the type of discharge will tend to be more solid

DR VERNON C DAVID (Chicago, Ill) I should like to endorse the early ileostomy, largely from the standpoint of some of the very serious things that happen in delayed ileostomy, and in which serious damage of the bowel has occurred My experience has differed somewhat from Doctor Bancroft's intimation that polyposis, occurring in chronic ulcerative colitis, is a favorable lesion We have recently had the opportunity of examining a colon which for many years had been ulcerated in which polyposis had occurred, and contrary to our usual view that these lesions are purely hyperplastic lesions of isolated areas of mucosa which have been preserved between the ulcers, one can trace not only hyperplastic lesions but also can find tumors which in all respects resemble papillomata and adenomata of the colon

One further remark about the undesirability of having late ileostomy The disagreeable complication of stricture and thickening of the bowel and the development of polypi has occurred in three of our patients who have developed, after long-standing ulcerative colitis, carcinoma of the colon We have, at the present moment, a woman in whom, about six months ago, we resected the transverse colon for carcinoma, who now has another carcinoma in the rectum So that these long-standing ulcerations with polyposis have really serious significance

DR EDWIN M MILLER (Chicago, Ill) Presented a slide of a child, age seven, with an intractable ulcerative colitis, in whom an ileostomy, after a six-month period of trial, has been eminently successful thus far After three months on the Medical Service, following an illness of seven months previously, she was referred to us The ileum, as one can see, was completely divided, and the skin flap brought together between the open ends of the bowel She has very rapidly picked up physically and mentally, and has become one of the happiest little patients we have in our ward at the County Hospital There has never been anything applied on the skin to prevent irritation, still the skin has always been in excellent condition She has spent most of her nights and a part of the time during the day face down upon a frame in which there is an opening, so that the contents of the proximal ileum drains directly into a receptacle, and during the day, at intervals, the nurse irrigates this area with a little sterile water

I do not know when, if ever, I shall be able to close this ileostomy, but I do have an idea that, after sufficient time has elapsed, I shall try to see what the colon will tolerate, by collecting some of the material from the proximal bowel and introducing it into the colon through a catheter, and having done that, over a sufficiently long time, without having evidence of a flare-up of the active process, I may find that the time will have arrived when we may close the ileostomy permanently

DR HENRY W CAVE (New York, N Y, closing) I do not agree with Doctor Stone in the question of performing ileostomies early If an ileostomy is to be established early, the simple method is to bring out a loop of the

terminal ileum, sew the loops together side-to-side, divide the loop, bring out the distal end at one end of the wound and the proximal end at the other end of the wound, as is done in the Devine procedure in the colon. Although I have not employed it, I believe it probably would be a simpler procedure than the one Doctor Stone has suggested. I firmly believe that patients showing early changes in the colon should have a prolonged and adequate medical supervision. Dr. Thomas T. Mackie, Director of the Grey Laboratories for the study of ulcerative colitis at the Roosevelt Hospital, has shown me patients with early changes in their colon that would seem as though they were going on to an irreversible stage. These patients, by medical management, have been cured for periods of seven to eight years. But it seems to me advisable that a conservative attitude should be taken in performing ileostomy too soon.

We have one patient, a male, age 50, whose disease started at the age of 25, and he has had the disease for 25 years. We have roentgenograms showing the start of the disease after 20 years. It was well into his rectum, but it traveled up his ascending colon into the splenic flexure, across his transverse colon and down to his cecum, and his terminal ileum is involved as well. He finally, after having had the disease for 25 years, submitted to ileostomy, and during these 25 years he has enjoyed very good health.

Another patient had an ileostomy performed eight years ago. She got along well, except during the fall, when she suffered from hay fever, at which time she would have profuse bleeding from the rectum. After eight years she finally submitted to a subtotal colectomy, and since that time has gained 16 pounds in weight. She, apparently, had been absorbing from this diseased colon and it was a menace to her. Therefore, after eight years, we felt that for her to be in better health the diseased viscus should be removed.

Doctor David has commented on the question of the incidence of carcinoma superimposed on chronic ulcerative colitis of the colon. From the literature, more than I can gather, I would say that 3 per cent of the patients who have reached an irreversible stage of pseudopolypoid degeneration will develop cancer.

THE SURGICAL MANAGEMENT OF CARCINOMA OF THE LEFT HALF OF THE COLON*

HOWARD C NAFFZIGER, M D

AND

H GLENN BELL, M D

SAN FRANCISCO, CALIF

FROM THE DEPARTMENT OF SURGERY, UNIVERSITY OF CALIFORNIA MEDICAL SCHOOL, SAN FRANCISCO, CALIF

IN MAKING A STUDY of lesions of the large intestine, we have considered separately those of the right side and those of the left side of the colon. The study of lesions of the right half of the colon was reported recently¹. Four cases, in which the tumor occurred directly in the midportion of the transverse colon, though analyzed separately, are included in the present study.

Seventy-eight patients with carcinoma of the left half of the colon and transverse colon (exclusive of the rectum) were treated at the University of California Hospital during the last ten years (1930 to 1940). Three of these had a second lesion of the colon, requiring separate resection, bringing the total to 81 cases. Of the 81, 32 received palliative treatment only, and 49 had resections. The operability of the whole series, then, was 60.4 per cent.

All of us realize the necessity for early diagnosis and treatment in dealing with any malignant condition. Failure to detect the disease early in its course may result from ignorance on the part of the patient. Too often it is directly attributable to carelessness on the part of the profession. The old teaching that blood in the stool or a change in bowel-habit means a lesion somewhere in the bowel is just as true as when it was first postulated. Perhaps it is even more important now, for not only have we diagnostic aids at hand, but operative means of relief as well for patients whose diagnosis is made early. It is the physician's responsibility to use every means at his command to find the source of the trouble.

Once the diagnosis is made, preparation for operation becomes of paramount importance. If the patient has an acute obstruction, it is obvious that his symptoms must be relieved at once either by an indwelling nasal tube into the stomach, or by some form of decompressive operation such as cecostomy or colostomy performed under local anesthesia. We prefer a combination of the two. The distention in the large bowel may be so great that there is danger of rupture of the cecum, and cecostomy may be necessary as an emergency measure. For patients who are not suffering from acute obstruction, some controversy exists as to whether or not cecostomy or colostomy should be performed some time before resection is undertaken. Some surgeons remove lesions of the descending colon or sigmoid in one stage, either with a cecostomy or colostomy at the same operation, or without decompressive

* Read before the American Surgical Association, St. Louis, Mo., May 1, 2, 3, 1940

operation of any type. In our opinion, however, resection of any portion of the left side of the colon with a primary anastomosis is very hazardous unless cecostomy or colostomy has been performed previously. Whether a colostomy is to be performed just above the lesion, or in the transverse colon, or a cecostomy is to be established, is a matter of choice for each surgeon. We usually prefer a cecostomy because it is a smaller procedure, it can be performed under local anesthesia, and the wound is easier to close. If properly made, it is adequate for cleansing the bowel before surgery. Our custom is to perform a cecostomy under local anesthesia. During the next ten to 14 days a nonresidue diet high in carbohydrates and vitamins is given, with transfusions of blood as needed to bring the blood picture to normal, daily washing of the bowel through the cecostomy and the rectum is carried out. One ounce of Epsom salts in eight ounces of water is given each morning for several days before the operation. The foregoing procedures allow the infection and edema of the proximal bowel and tumor to subside, thereby making the suturing safer. Two days before surgery, 1 gr lead and opium pills are given three times a day to reduce the intestinal activity. When possible, these patients are permitted to be up and around rather than at complete rest in bed. Such a regimen brings the patient to the best possible condition before resection is undertaken. The patient who is gaining weight is a much better risk than one who is losing weight, and the time taken for preparation before resection is well spent.

The choice of anesthetic depends on the age, general condition and temperament of the individual patient, as well as on the location of the tumor. Spinal anesthesia is not used for a lesion in the splenic flexure, but is used for lesions lower down. The transverse incision, described by Hoag,² is of great advantage in the removal of a tumor of the splenic flexure or the descending colon.

It should be apparent that no single type of operation is applicable to all lesions of the left side of the colon, one of a number of different procedures may be employed according to the necessities of the case. The type of operation chosen depends upon many factors—the age and general condition of the patient, the location and fixation of the tumor and the preference of the individual surgeon. If it is true that the method sometimes depends more upon the preference of the surgeon than upon the other factors, it is equally true that the method is not so important as the man behind it. One surgeon may use clamps for the anastomosis, another may use the open method. Each may be right, depending upon his training and experience. In training a resident staff, however, it is important to teach one method of resection and anastomosis well.

In this group of 49 operations there were 13 Mikulicz procedures, three Rankin obstructive operations, three Hartmann procedures, 22 end-to-end anastomoses, and eight side-to-side anastomoses.

The Mikulicz procedure does not permit the removal of so much lymphatic-bearing tissue as a more extensive resection, and a longer period of time is required for complete closure when this procedure is used. The Hartmann

operation is employed only when the lesion is so low as to preclude an anastomosis to the short distal stump of bowel which remains, or when the general condition of the patient does not warrant an abdominoperineal resection. This procedure has the advantage that the perineum and the nerve supply to the rectum and bladder are left intact. Rankin's obstructive operation need not be done if a previous colostomy or cecostomy has been performed as indicated above. We prefer to do an anastomosis.

Our choice of operation is resection, after the careful preparation described above, followed, if possible, by either an end-to-end or a side-to-side anastomosis by the open method. In performing the resection, we free the bowel beyond and below the lesion, using as wide a margin as possible and taking a large section of mesentery with the tumor. After the point of transection has been determined, the flow of the fecal stream is controlled by the use of broad rubber bands around the bowel rather than the use of clamps. The blood supply to the large bowel is so precarious that the use of clamps may injure it to the extent of causing thrombosis in the vessels, with delayed healing and even leakage. The bowel is transected with the electrocoagulation unit and, if a side-to-side anastomosis is to be made, the ends are turned in with catgut sutures and reinforced with Halsted mattress sutures. The loops of bowel are then held in approximation by stay sutures of silk and the first posterior row of interrupted silk sutures is placed and tied. The Halsted mattress sutures of silk are laid anteriorly and retracted over the stay sutures. The opening into the bowel is made with the electrocoagulation unit adjusted so that the coagulation will control all bleeding. This prevents contamination of the suture line by blood from the incision into the bowel. Local peritonitis around the line of sutures predisposes to the breakdown of the anastomosis with subsequent leakage, general peritonitis and death. A row of continuous catgut sutures is placed posteriorly, taking the full thickness of the bowel, and is tied. The row of sutures previously laid anteriorly is tied and reinforced with interrupted Lembert sutures of silk. The anastomosis is further protected and walled-off from the small bowel by the omentum. The abdomen is closed without drainage. Essentially the same technic is used if an end-to-end anastomosis is performed.

Five deaths occurred among the 49 patients, a mortality of 10 per cent. This compares favorably with the operative mortality in the 27 lesions of the right side of the colon (Table I). If the 49 operations are divided according to their positions as transverse or left, it is seen that the mortality for lesions on the left side of the colon drops to 8.8 per cent (Table I).

Of the five patients who died, one, a woman, age 47, succumbed suddenly on the seventh day after operation, presumably from pulmonary embolus. This patient had had a cecostomy, followed in eight days by a resection with a side-to-side anastomosis. Her course after operation had been remarkably smooth until the seventh day when, upon turning over in bed, she suddenly died. Unfortunately, autopsy was not permitted, but the clinical picture was that of massive pulmonary embolus.

TABLE I
COMPARATIVE MORTALITY OF RESECTION OF CARCINOMATA OF THE
LARGE INTESTINE

	No of Cases	No of Deaths	Mortality Percentage
Right colon	27	3	11.1
Transverse colon	4	1	25.0
Left colon	45	4	8.8
Totals	76	8	10.5

Four patients died from peritonitis, one, a woman, age 48, had severe anemia, a blood pressure of 210/114, and a considerable loss of weight before operation. She died on the twelfth day after a Hartmann procedure, as the result of wound infection, peritonitis, paralytic ileus, and hypertensive heart disease. Autopsy was not permitted. This patient might have been saved by the performance of a cecostomy or colostomy two weeks or so before the resection.

A man, age 65, died of peritonitis on the fourth day after a Rankin obstructive resection. This patient had had a cecostomy two weeks before resection. At operation, it was demonstrated that the tumor of the splenic flexure had perforated into the lateral abdominal wall, forming an abscess. There were metastases to the liver. Autopsy was secured in this case.

Another man, age 48, died on the fifth day after a resection and end-to-end anastomosis which was performed ten days after a cecostomy. The lesion was adherent to the bladder and the repair of the wound in the bladder broke down. Apparently this was the source of the infection as, at autopsy, the anastomosis proved to be intact.

The fourth patient to die of peritonitis succumbed four days after resection and end-to-end anastomosis of the transverse colon, which was followed immediately by a tube cecostomy. Metastases to the omentum were present. In this case the anastomosis broke down, as proved by autopsy. This patient, too, might well have survived surgery if a cecostomy had been established well in advance of the resection.

In the group of five surgical deaths, then, two patients might not have died had the proper preparation and treatment been instituted before resection was performed. In the last three cases, the lesions might fairly be classed as inoperable. Nevertheless, in our opinion, resection was justified, even though cure could not be expected. If such patients survive surgery, their chances for comfort during the remainder of their lives are so much improved that resection, even without hope of cure, is reasonable.

Adenocarcinoma was found in all 49 cases, 29 lesions occurred in the sigmoid colon, ten in the splenic flexure six in the descending colon and four in the transverse colon.

Of the 49 patients, 33 are now living and well, three are living but have metastases, and 13 have died (five following surgery and eight after varying

periods of time, Table II) These eight patients had no gross or microscopic evidence of metastasis at the time of surgery, yet they died of metastases in from six months to four years, three others are still living, but have metastases Of these 11 patients, seven had resection with end-to-end anastomosis, two had the Mikulicz operation, one had Hartmann's resection, and one, Rankin's obstructive resection This result is discouraging and raises the question whether the resections have been sufficiently extensive to remove all the lymphatic-bearing area In our opinion, there is a tendency to remove too little rather than too much especially when an immediate anastomosis is planned

TABLE II

RESUME OF PROGNOSIS OF CARCINOMATA OF THE LEFT HALF OF THE COLON—49 CASES

	Opera- tive	Less than 1 yr	1-2 yrs	2-3 yrs	3-4 yrs	4-5 yrs	5-6 yrs	6-7 yrs	7-8 yrs	No of Cases
Living and well		6	6	7	2	5	4	2	1	33
Living, with metastases				1	1		1			3
Dead	5	3	2	2	1					13
Total										49

For the future, our plan is to perform a much more extensive resection of the bowel and the mesentery in patients who show no gross evidence of metastases at the time of surgery We know that the spread is upward and toward the midline By performing the more extensive removal we may be unable to effect an anastomosis at the time of resection, but in some instances the bowel can be reunited at later operation At least we shall hope to cure more of these patients

SUMMARY

A study of 49 cases of carcinoma of the left half of the colon is reported The deaths in this series are analyzed and suggestions are made as to how they might have been prevented Our method of caring for patients with disease of the left half of the colon is outlined

REFERENCES

- ¹ Bell, H Glenn, and Henley, R Bruce Right Colectomy in One Stage Surgery, in press
- ² Hoag, Carl L A New Approach to Resection of Cancer of the Colonic Flexures California and West Med, 45, 148, August, 1936

DISCUSSION—DR JOHN A WOLFER (Chicago, Ill) I am very happy to hear this report, and there are two or three points that I would like to stress First is the preoperative preparation I think that very frequently—too frequently—we push these patients suffering from carcinoma of the colon into a very serious, difficult, and long operative procedure without adequate preparation We have been using over a period of years rather meticulous care, first, in the type of diet in attempting to reduce the putrefying organisms in the colon, giving a high carbohydrate and basal protein diet, and secondly, resorting to copious flushing of the colon in those cases that are not com-

pletely obstructed and can be cleansed. Such a regimen may require as much as six to 12 days, which I think is time extremely well spent, as has already been brought out.

The second is a procedure that I have employed during the past two or three years. After the bowel has been sectioned, for instance, in doing an end-to-end anastomosis of the left colon, we thoroughly cleanse the cups of the sectioned ends with water or salt solution followed with 5 per cent carbolic acid and 50 per cent alcohol. This seems like empiric treatment, but it came about in this way. In discussing the matter of the high mortality in colon resection with Doctor Ivy, he stated that in all his colon work upon dogs he had a tremendous mortality from infection until he began using a procedure of this type. He uses 5 per cent carbolic acid and 80 per cent alcohol, touching the edge of the cut bowel wall with 95 per cent carbolic acid. That seemed a little too diastolic to me, so I compromised by using weaker solution of alcohol and omitting the 95 per cent carbolic acid.

Whether this procedure is as beneficial as I think it is, remains to be proven. However, in one instance in which we performed a resection of the sigmoid with a primary end-to-end anastomosis, with a tube decompression, I had the opportunity of seeing the abdominal cavity about one year later because of some complication that had arisen. I was unable to find the site of the anastomosis which had been performed previously, even though I could judge very well its location from the site of fixation of the colon to the abdominal wall due to the tube implantation. The lumen of the bowel was not narrowed, there was no evidence of any cicatrization, no adhesions were present, and the intestine looked perfectly normal. I am reporting this for what it may be worth. I am employing the procedure in every case of large bowel resection, and have no reason to feel other than that it is of great advantage in preventing infection of the bowel wall and contamination of the peritoneal cavity.

I am also pleased to hear the authors speak of the care in limiting the number of sutures in performing the anastomosis. I agree, thoroughly, that we destroy more lives by using a large number of sutures than we save, since each time a suture is placed through the intestinal wall a slab culture is made by carrying infectious material into the wall. Then, by tying the suture ischemic necrosis is produced. The inoculation, in the presence of devitalization, provides the essentials for infection and further necrosis. If too many sutures are placed, need we wonder why leakage takes place at the site of the suture?

We are employing one other precaution, which I believe is worth while, namely, that immediately after an intestinal resection, a gastric tube is inserted and aspiration begun at once after the operation. Wangenstein has shown that the largest amount of air or gas in the intestine consists of air that has been swallowed, and it seems logical that if the swallowed air is constantly aspirated, the intestines, in the majority of cases, can be kept perfectly deflated. This we have demonstrated to ourselves on numerous occasions.

Another point is on some work that we have recently introduced on vitamin C deficiency in surgical patients. We have found that many of the cases of malignancy have a high grade vitamin C deficiency—many in the scurvy level. Formerly, we made blood vitamin C determinations in all cases but because of the almost uniform vitamin C depletion found, all patients are now given 1,000 mg. of ascorbic acid intravenously preoperatively for a number of days, and then postoperatively during the first week or ten days until the wounds are well healed. We believe that this is another factor that will make the operative procedure safer and no doubt facilitate wound healing.

IRRADIATION BURN OF THE INTESTINE*

WILLIAM CRAWFORD WHITE, M D

NEW YORK, N Y

FROM THE SURGICAL AND GYNECOLOGIC SERVICES, ROOSEVELT HOSPITAL, AND THE GYNECOLOGIC SERVICE,
WOMAN'S HOSPITAL, NEW YORK, N Y

AT THE PRESENT TIME, the accepted method of treatment of carcinoma of the cervix uteri is with interstitial radium and surface applications in the vagina, followed by high voltage roentgenotherapy to the pelvis. As a result of this technic, certain complications have been observed. In the present communication we will confine our attention to injury to the large and small intestines by irradiation. It is the impression of many that this complication is on the increase, and, furthermore, that this increase has been due to the heavier doses of radium and roentgenotherapy that have been administered in recent years. When inquiry into the relative rôle of radium and roentgenotherapy is started, one immediately encounters contrary opinions, but the author feels that the weight of evidence is in favor of radium being the chief factor. It is not, however, the purpose of this paper to further discuss this problem of the gynecologist and the roentgenologist. Rather, we plan to deal with the complication as a definite fact and shall attempt to discuss its diagnosis and treatment from the general surgeon's point of view.

Mild proctitis after treatment of the carcinoma of the cervix is not infrequent. The patient may have diarrhea, tenesmus and abdominal cramps. Proctoscopic examination will reveal hyperemia of the mucous membrane, especially at the level of the cervix. With the passage of the instrument, it is not unusual to have a little bleeding. By palpation, the mucous membrane feels soft. With palliative treatment this condition usually clears up and leaves a normal appearing mucous membrane.

Beyond this comparatively mild reaction of the mucous membrane, more severe injury to the tissue may be seen, in which the clinical symptoms become more severe, with the additional symptoms of blood and mucus in the stools. Proctoscopic examination will then reveal severe congestion of the mucous membrane with patches of ulceration. These ulcers, at first, will present soft edges to palpation, and, to vision, will show a dirty gray slough on the surface. The ulcers bleed easily on examination. Todd¹ has reported further changes in these ulcerated areas in which the edges have become so hard to digital examination, and resembled carcinoma so much, that she has referred to them as "pseudocarcinoma of the rectum." She reports several that were thought to be carcinoma of the rectum until biopsy had proved them to be otherwise. Todd also reports another type of extrinsic injury to the perirectal tissues, with secondary involvement of the rectum. In this second

*Presented by Title before The American Surgical Association, St. Louis, Mo., May 1, 2, 3, 1940.

group, the pelvis may feel frozen, as if there had been a massive invasion of carcinoma. She reports that "the histology of both types of lesions have a striking feature in common, namely, vascular occlusion throughout, and it suggested that this phenomenon may be the vital one concerned—irradiation causing thrombosis in some of the smaller branches of the hemorrhoidal vessels, and this, spreading, leads to obliteration of the blood supply of the rectum in the junctional region, followed by the occurrence of infarction and mucosal ulceration."

Some of these cases ulcerate into the vagina to cause rectovaginal fistulae or into the perinectal tissue to cause perinectal abscesses that require incision and drainage. With palliative treatment, most of the patients with ulcer and rectovaginal fistulae will clear up and leave a smooth mucous membrane. But some will have a submucous scar formation that will constrict the lumen of the rectum—enough to interfere somewhat with stools but not enough to obstruct.

In the severe cases, colostomy may be indicated to give relief from pain and to reduce the infection in the rectum by diversion of the fecal current.

CASE REPORTS

Case 1—Woman's Hospital No 64177. Carcinoma of cervix. J. D., age 32, female, was treated with radium, May 8, 1937, followed by high voltage roentgenotherapy. Re-admitted, April 11, 1939, with history of intermittent lower abdominal cramps (severe enough to force her to go to bed) and obstipation, suggesting partial ileus. Barium enema showed an area of narrowing, 4 cm long, at the rectosigmoid junction. The narrowing was smooth and the appearance was strongly suggestive of a localized radium proctitis.

Operation (W. C. W.)—April 15, 1939. Many peritoneal adhesions were found. The lower four inches of the sigmoid colon and part of the rectum just below the peritoneum were thickened and indurated. The peritoneal surface of the sigmoid showed white areas with punctuate red spots scattered throughout. There was no suggestion of metastases. A Mikulicz colostomy was performed, and the patient allowed to go home. She returned to the hospital in March, 1940, for closure of the colostomy. Sigmoidoscopy of the rectum through the anus, and of the sigmoid through the colostomy, revealed healthy looking mucous membrane, but some tubular contracture of the bowel. The sigmoid just admitted a seven-eighths-inch sigmoidoscope. The colostomy was closed, April 1, 1940. She was discharged, April 17, 1940, with a well-healed abdominal wound, and has been having normal bowel movements since.

It is easy to believe that radium may be the causative agent in injuries to the rectum, while the same may be said of the injury to the intestine that becomes adherent to the cervical stump.

Case 2—Roosevelt Hospital No 352464. S., age 69, female, had had a supravaginal hysterectomy 35 years before she developed a carcinoma of the cervical stump. For this she was treated with radium and high voltage roentgenotherapy. After this she had proctitis for a short time. Six months later, she began to have lower abdominal cramps, and, one month after this, came in with acute ileus. Plain films disclosed distention of the small intestine with fluid levels in various dilated loops.

Operation (W. C. W.)—It was discovered that the ileum was adherent to the peritoneum over the cervical stump. When brought into the wound, the ileum was

found to have a marked cicatricial contracture with induration, about a foot from the ileocecal valve. The ileum was resected, and a lateral anastomosis established. The specimen of the resected ileum showed an ulcer of the mucous membrane, 1x1.5 cm, with complete contracture and obstruction at this point. Microscopic study revealed no evidence of malignancy but well-defined irradiation necrosis of the ileum. (The patient died three days later, after she had developed mesenteric thrombosis that extended 200 cm up the ileum from the site of the anastomosis.)

This case illustrates the grave risk involved in treating, with radium, a cervical stump without knowledge of the presence or absence of intestinal adhesions to the peritoneal side of the stump. It is suggested that one method of study that might be employed to see if the intestine is free, would be to have an intestinal barium series with a radiopaque substance in the vagina, in order to demonstrate the relationship. In certain cases, an exploratory celiotomy, to guard against this hazard might be justified.

We now come to another group in which there is more reason to believe that high voltage roentgenotherapy may play a part in the damage that has been initiated by the radium. We refer to irradiation burn of the sigmoid, of which the author has had three instances. In our cases, the symptoms have come on six to eight months after treatment. T. E. Jones³ has reported one such case as late as eight years after therapy. The history of these patients was similar, in that they all had diarrhea, cramps, bloody stools, and lower abdominal tenderness. All had evidence of incomplete ileus at first, and one went on to complete obstruction. A short review of each case will give best the pathology and problems to be met.

Case 3—Woman's Hospital No 65373. Carcinoma of cervix. J. L., age 35, female, was admitted, October 17, 1937, for radium only. For a short time after this treatment she had moderate proctitis. She was readmitted, July 15, 1938, with a complaint of lower abdominal cramps, bloody stools, nausea and vomiting. Barium enema showed a smooth narrowing, about one inch in length, of the proximal sigmoid.

Operation (W. C. W.)—A large mass was found in the upper portion of the sigmoid colon. It felt like a rubber tube. The serosa had pearly-white patches with dotted areas of telangiectasis. Ten centimeters of bowel was resected by the Gibson-Balfour technic.

Pathologic Examination—Gross The opened specimen revealed an ulceration of the mucous membrane, 2.5 cm in diameter. The wall of the bowel in the region of the ulcer was transformed into scar tissue extending slightly beyond the necrosis of the mucous membrane. In April, 1940, the patient was in excellent health.

Case 4—Woman's Hospital No 68865. Carcinoma of the cervix. H. W., age 51, female, was admitted, March 6, 1939. Treated with radium and high voltage roentgenotherapy. She was readmitted, September 23, 1939, with a diagnosis of intestinal obstruction. Three weeks before admission she began to have lower abdominal cramps, diarrhea, and bloody stools. For this she had been taking barium by mouth. This had apparently not been passed, but had accumulated, dried, and initiated a complete obstruction. A cecostomy was performed by Dr. A. J. Murphy. Later, a sigmoidoscopy revealed, 13 cm from the anus, a moderate constriction of the rectum with edema of the mucous membrane. Through this constricted ring one could see ulcers in the rectum above.

Exploratory Celiotomy (W. C. W.)—October 16, 1939. The uterus was fixed by a low-grade inflammatory reaction. Attached to its posterior surface, as well as to both broad ligaments, was the sigmoid colon. On separating the sigmoid from the posterior

uterus, a necrotic area was entered which contained free pus. The colon had the typical appearance of irradiation burn with patches of pearly-white serosa, and telangiectases. The sigmoid had the feel of a rubber tube. As the process involved the rectum also, it was decided to establish a colostomy in the healthy upper sigmoid. The patient did fairly well after the operation, but died of a secondary hemorrhage of the lower bowel, 34 days postoperative.

Case 5—Woman's Hospital No 66805. Cancer of cervix, Grade II. M A G, age 37, female. Treatment was instituted, May 11, 1938, when radium and high voltage roentgenotherapy were administered. She was readmitted, October 16, 1938, complaining of diarrhea of several weeks' duration and lower abdominal cramps. Barium enema showed a smooth narrowing of the distal sigmoid, involving about two inches of the bowel, with a maximum caliber in this area of about one-half inch. Above and below this narrowing the bowel showed normal contour.

Operation (W C W)—October 17, 1938. The sigmoid was found free in the abdominal cavity. It was greatly thickened and slightly kinked at one point. For a length of four inches, the serosa had a pearly-white color with telangiectatic spots scattered throughout. The thickened area was six inches in length. There was marked edema of the mesentery. There was no obvious point of necrosis in the wall. A resection of the involved area was performed, and the Gibson-Balfour anastomosis established.

Pathologic Examination—*Gross*. The opened specimen revealed an ulceration of the mucosa with tissue destruction which seemed to penetrate beyond the muscular layer in areas. The muscularis was thickened to 1.2 cm. The serosa also was thickened. *Microscopic*. Necrosis and acute inflammatory reaction were demonstrated about the ulcer. The capillaries showed distention and congestion.

The patient, in April, 1940, was in excellent general condition, with the exception of a minute fecal fistula of the abdomen which apparently refused to heal. This may be due to some irradiated bowel that has deficient reparative power.

From a consideration of these cases and further thought on the nature of the pathology of this disease, the author is inclined to believe that the procedure to be employed must vary according to conditions encountered. This is influenced by the extent of the necrotizing process, with the possibility of perforation of the intestinal wall and consequent peritonitis. In one of the above cases, perforation had occurred, and in such a problem the author believes that a colostomy of either the transverse colon or the upper sigmoid colon is indicated, together with drainage of the abscess cavity. If the patient survives the operation, there is excellent prospect that the mucous membrane will gradually heal, since it is freed from the infective fecal current. Undoubtedly, there will be some contracture of the lumen of the bowel. If this is sufficient to cause obstructive symptoms, resection of that part of the bowel may be necessary. The caliber of the lumen and the condition of the mucous membrane can be determined by sigmoidoscopic examination through the colostomy wound if it is in the upper sigmoid. Barium study for evidence of obstruction and the size of the lumen may be attempted.

When the irradiation burn involves the rectosigmoid, the operation of choice is a Mikulicz colostomy with a well-formed spur. The process may subside sufficiently to permit later closure of the colostomy.

If the irradiation burn is localized in the free portion of the sigmoid that is well covered with peritoneum, a resection, with end-to-end anastomosis, is the operation of choice. Because of irradiation occlusion of blood vessels it

is very important to go sufficiently wide of the lesion to assure good blood supply

In addition to the ileum that was attached to the cervical stump when it received the radium burn, we have had two cases at the Roosevelt Hospital in which there was irradiation burn of ileum that must have been some distance from the cervix. T. E. Jones³ has reported two such cases

Case 6—Roosevelt Hospital No 383053 Epidermoid carcinoma of cervix, Grade II T. S., age 35, female, was admitted, July 26, 1938, and treated with radium and high voltage roentgenotherapy. On January 30, 1939, the patient returned with a history of intermittent attacks of lower abdominal colic followed by nausea and vomiting of 48 hours' duration. Gastro-intestinal series revealed "a narrow area of the ileum, eight inches from the cecum, with partial obstruction both to the regurgitated enema and to the barium meal. The appearance suggested organic bowel lesion from irradiation."

Operation (Dr W. E. Alsop—W. C. W. present).—Fourteen inches from the ileocecal valve, a signet-ring contracture of the ileum, about three-quarters of an inch wide, was found. The bowel at this point was ischemic, and the wall of the intestine thickened. Some three inches distal to this, there was a pale disk-shaped area, three-quarters of an inch wide. There were at least four such ischemic areas in the mesentery of the ileum, also, some areas were seen on the sigmoid. The distal 24 inches of the ileum was somewhat thickened and edematous. Seven inches of ileum was resected, and a lateral anastomosis established. In April, 1940, the patient was in good health.

Case 7—Roosevelt Hospital No 384363 B. W., age 53, female, was admitted, October 29, 1938. The patient had been treated for carcinoma of the cervix with radium and roentgenotherapy, nine months before, in California. Her complaints were nausea, vomiting, and abdominal pain. Gastro-intestinal series disclosed an ulcer of the duodenum and a narrowed terminal ileum proximal to the ileocecal valve. She was allowed to go home, and was readmitted in December, 1938, with the history that she had had constant epigastric pain, not related to food. For one week before admission, she had vomited frequently. Another gastro-intestinal study revealed an obstructive process of the small intestine, which was difficult to localize.

Operation (Dr F. H. Amendola).—The head of the cecum and the terminal ileum were firmly adherent to the right pelvic brim. In dissecting this mass away, so that it could be delivered into the wound, a small abscess was encountered, which communicated directly with a large defect in the ileocecal ring, one inch in diameter. The ileocecal ring was almost stenosed as a result of fibrous contracture. The terminal ileum and proximal third of colon were resected, and a lateral anastomosis established. Pathologic examination showed chronic inflammation of ileum with ulceration of the mucous membrane. The patient died, 16 days later, of peritonitis.

CONCLUSIONS

Irradiation burn of the intestine is a definite complication of irradiation treatment of carcinoma of the cervix. The damage to the intestine appears to be related to the amount and method of dosage as well as to the susceptibility of the patient.

The gross and microscopic pathology has been described in the course of the article. From the clinical viewpoint, it is to be noted that our cases have shown destructive action of all the coats of the intestine, although the mucous membrane, it is true, appears to be the most sensitive. When ulceration occurs in the rectal mucous membrane, it may eventually erode through

the entire wall to cause perianal abscess or rectovaginal fistula, or peritonitis when the intestine is within the abdominal cavity. If no perforation occurs, the ulcer may gradually heal up and leave an intact mucous membrane. Usually, the thickening due to fibrosis in the musculatus persists so as to reduce the caliber of the bowel. This process may go on to complete obstruction. It is interesting to note that in all our obstructive cases ulcers of the mucous membrane were present.

In mild injury to the rectum and sigmoid, palliative treatment is indicated, in the more severe cases, colostomy should be employed, in order to permit diversion of the fecal current so that the infected ulcers may have more chance to heal. Later, if this treatment is successful, the colostomy may be closed.

In localized injury to the sigmoid or ileum, resection is the method of choice.

It is the author's opinion that the injury to the sigmoid and ileum is more common than the records would indicate. The author strongly suspects that, occasionally, the opportunity to help a patient has been missed because the symptoms have been interpreted as those of a hopeless intra-abdominal recurrence. Gynecologists and general surgeons should be alert to this possibility, for success in treatment depends on early diagnosis and timely intervention, with procedures such as colostomy or resection.

Appreciations and thanks are expressed to Dr W. E. Alsop and Dr F. H. Amendola for permission to report their cases at the Roosevelt Hospital, also to Dr A. H. Aldridge, Director of the Woman's Hospital, for his kindness and cooperation in the care of their cases.

REFERENCES

- ¹ Todd, T. F. Rectal Ulceration Following Irradiation Treatment of Carcinoma of the Cervix Uteri. *Surg, Gynec and Obstet*, **67**, 617-631, November, 1938.
- ² White, W. C. Acute Intestinal Obstruction Following Radium Treatment of Cervix Uteri. *ANNALS OF SURGERY*, **105**, 292-295, February, 1937.
- ³ Jones, T. E. Intestinal Complications Resulting from Prolonged Radium and X-ray Irradiation for Malignant Conditions of Pelvic Organs. *Amer Jour Obstet and Gynec*, **29**, 309-316, 1935.

EXPERIENCES IN CLEFT PALATE SURGERY*

ROBERT H. IVY, M.D.

PHILADELPHIA, PA.

IN 1934, we⁶ published a paper on this subject, referring especially to the technical methods of Veau⁸ and Doiran⁵. Since that time, in our opinion, further advances have been made in these procedures, which have led to some modification of our operative methods. The principal work which has had this modifying influence is that of Axhausen,^{1,7} who recognizes the validity of the objections to the classic Langenbeck operation that have been advanced particularly by Veau. According to Veau the essentials for satisfactory results in cleft palate operations are (1) An epithelial covering on the nasal side, as well as on the palatal side of the flaps, (2) obliteration of the dead space above the palatal flaps, and (3) suture of the separated palatal muscles. Axhausen has so modified the Langenbeck technic as to satisfy these requirements to a considerable degree. The technic of the operation, in the early stages, does not differ materially from that of the typical Langenbeck operation. A lateral incision is made on each side of the hard palate close to the teeth, from the tuberosity forward, and the mucoperiosteum is separated from the bone almost to the margin of the cleft. The hamular process is exposed in the lateral incision and separated with a chisel to allow the tendon of the tensor palati to be carried toward the median line, thus relaxing the soft palate. At this point, Axhausen isolates, ties and severs the palatine artery near its emergence from the foramen. The succeeding steps diverge materially from the classic operation. At the cleft margin the nasal mucosa is carefully separated from the bone to form a free flap of this tissue on each side. At the posterior edge of the hard palate, instead of cutting the nasal mucosa right through together with the aponeurosis, the continuity of this mucosa over to the soft palate is preserved, but the bony edge is carefully freed of soft tissue submucously. The free edges of the soft palate are not pared but are split to form broad raw surfaces (Fig. 1). It then becomes possible to suture the nasal mucosa across the cleft in a continuous layer from the tip of the uvula to the anterior margin of the cleft (Fig. 2). The muscles of the soft palate are then united in the median line with several catgut sutures (Fig. 3). Finally, the oral mucosa from back to front is sutured as a separate layer (Fig. 4). Packing is placed in the posterior part of each lateral incision, and Axhausen then covers the field of operation with a previously prepared celluloid plate fitting over the teeth, to hold the flaps up against the bone. We do not consider this support at all necessary, since the desired purpose is accomplished by the soft tissue sutures. Figures 5 and 6 illustrate, diagrammatically, the difference in result of the classic Langenbeck operation

* Presented by title before the American Surgical Association, St. Louis, Mo., May 1, 2, 3, 1940.

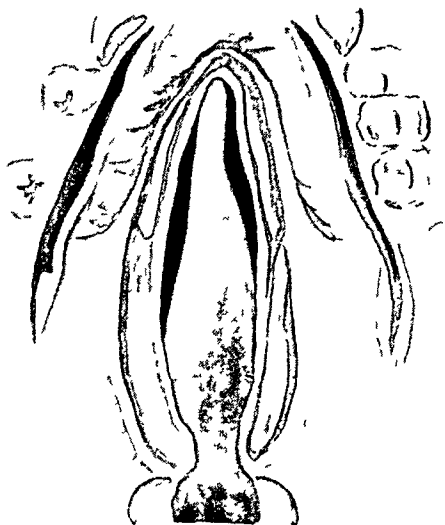


FIG 1—Bony edges of hard palate cleft freed of mucoperiosteum on nasal and oral sides. Posterior border of hard palate also freed of soft tissues submucously. Edges of soft palate split. (After Axhausen)

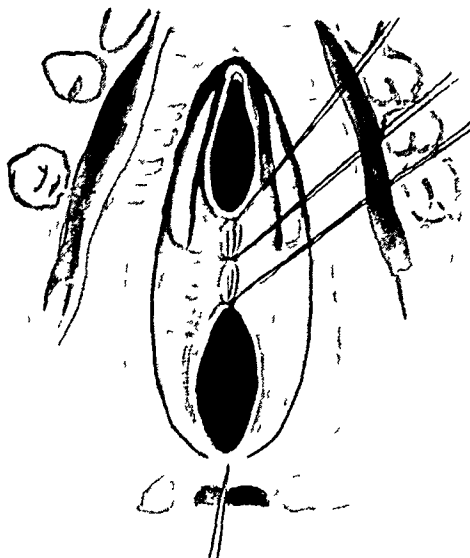


FIG 2—Sutures being placed in layer of nasal mucosa (After Axhausen)

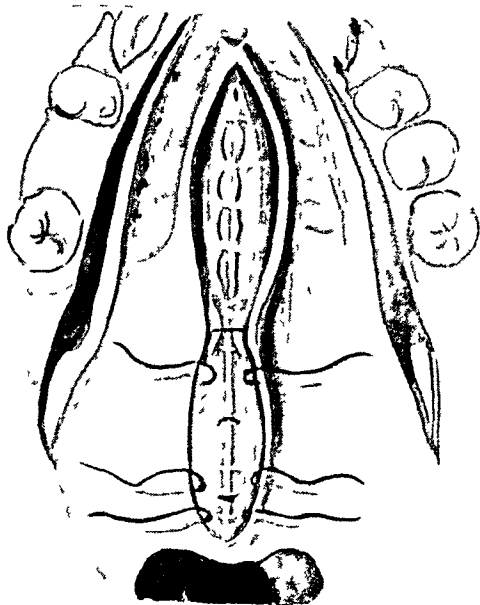


FIG 3—Sutures placed in muscular layer of soft palate (After Axhausen)

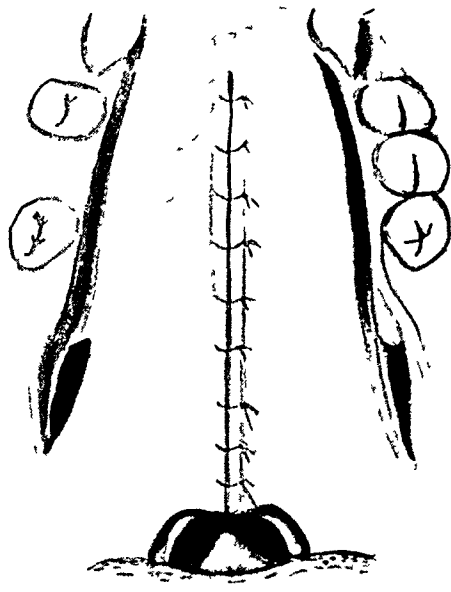


FIG 4—Layer of oral mucosa sutured (After Axhausen)

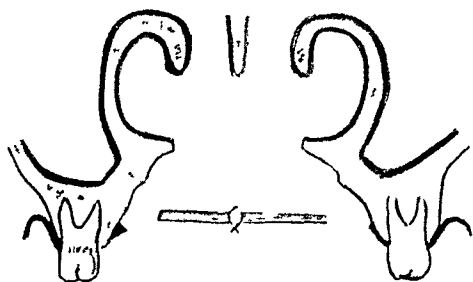


FIG 5—Diagrammatic cross section showing palatal flaps sutured in classic Langenbeck operation. These flaps are not epithelialized above and there is a dead space between them and the bone (After Axhausen)

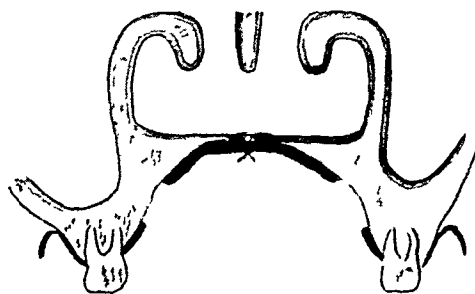


FIG 6—Diagrammatic cross section showing flaps after suture in separate layers by Axhausen technique. Nasal mucosa is intact above and flaps are in close contact with bone so that dead space is minimized (After Axhausen)

and that of Axhausen. In the former, the nasal surfaces of the flaps are not epithelialized and there is a dead space between the bone and the upper surfaces of the flaps. In the latter, epithelium covers both oral and nasal surfaces of the flaps and the dead space is obliterated. This results in better healing with less scar tissue and less retraction and shortening of the soft palate.

During the past three years, we have employed this technic in the closure of all posterior clefts of the palate, with the exception of those falling in the class of velopharyngeal insufficiency. In clefts originally extending completely through the anterior part of the hard palate and alveolar process to the lip, either unilateral or bilateral, we still continue to deal with this anterior portion by the Veau turnover flap of mucosa from the vomer, later using the Axhausen technic for the posterior closure.

In classifying cases of cleft palate from the standpoint of operating, we find it convenient to divide them into three groups: (1) Unilateral cleft of hard and soft palate, usually associated with unilateral cleft lip, (2) bilateral cleft of hard and soft palate, usually associated with bilateral cleft lip, (3) median cleft of soft palate usually extending a varying distance into the hard palate. These are the types most commonly found, but combinations and modifications occur occasionally.

We shall now consider these different types and take up the procedures which we have found to be most satisfactory in the treatment of each type.

(1) *Complete Unilateral Cleft of Hard and Soft Palate, Associated with Unilateral Cleft Lip*—Here, the cleft begins at the uvula, in the median line, extends forward through the soft palate, then passes on one side of the septum of the nose, the mucosa covering the vomer being continuous with the hard palate mucosa on the side opposite to the cleft. When the cleft reaches the alveolar process in front, it passes to one side of the premaxilla, and involves the lip on that side, the cleft in the lip usually passing completely through the floor of the nostril. The cleft may vary very greatly in width, and there is also a varying amount of distortion of the premaxilla, the side of this bone next to the cleft usually projecting forward. This distortion of the premaxilla has led surgeons to perform surgical reduction by cutting the bone through its attached side and fastening it back across the alveolar cleft with a wire suture. This in our opinion is entirely unnecessary, and is frequently harmful, causing undue flattening of the bone and upper lip and injury to tooth germs. This bone will usually assume correct position in time by pressure of the closed lip if the lip cleft be closed at an early age.

In this type of case, we advocate the following procedures. At from six weeks to three months of age, we combine the first-stage Veau operation on the hard palate and alveolar cleft with closure of cleft in the lip. The Veau procedure should be performed before the lip is closed, since this will nearly always insure complete closure of the cleft in the alveolar process all the way

to the front under the lip. If the lip is closed first, it is quite difficult to obtain this complete closure in front beneath the lip. The Veau technic has been frequently described,⁸ but a brief resume may not be out of place. Use is made of a flap of mucoperiosteum from the vomer, this flap being turned over so that its epithelial surface faces upward to form the lining of the floor of the nose on the side of the cleft, from near the posterior end of the hard palate to the cleft of the lip anteriorly (Fig 7). On the short side of the cleft, a palatal mucoperiosteal flap is completely detached at its anterior end, raised from the bone from before backward, and swung across the cleft, with

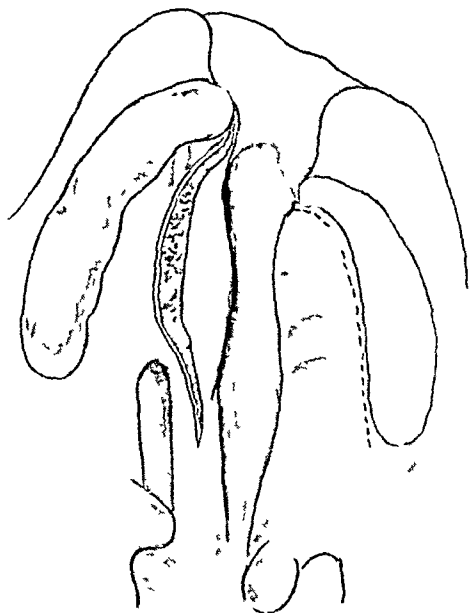


FIG 7—Flap of mucoperiosteum from vomer being raised. Mucoperiosteal flap from outer side of hard palate outlined. (After Veau)

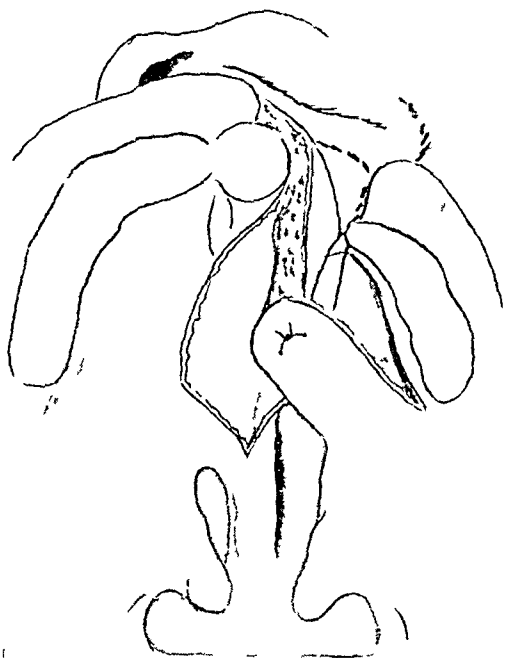


FIG 8—Flap from vomer turned over to form floor of nose and palatal flap from opposite side of cleft swung over and sutured to it. (After Veau)

its raw surface applied to the raw surface of the vomer flap (Fig 8). These two flaps are held together with one or two through-and-through silk sutures. The nasal mucosa on the short side of the cleft is loosened from the bone for a distance and turned over, so that it can be sutured to the anterior end of the vomer flap, thus closing the cleft under the lip (Fig 9). The operation is now completed by closure of the lip cleft by the Blain-Minault² technic. This raising and shifting of flaps creates considerable raw surface in the hard palate, but this rapidly heals over, leaving only a cleft in the soft palate and posterior part of the hard palate, to be closed not before two and one-half to three years of age by the Axhausen method, already described.

(2) *Complete Bilateral Cleft of Hard and Soft Palate, Associated with Bilateral Cleft Lip*—Here, the cleft extends in the midline through the uvula, soft palate and hard palate, with the lower border of the septum of the nose lying free in the cleft, so that there is a communication with both sides of the nose. On each side of the premaxilla the cleft extends through the alveolar

process and lip. The anterior end of the vomer bearing the premaxilla is frequently elongated, carrying the premaxilla and philtrum of the lip abnormally far in advance of the lateral portions of the maxilla and lip. Here also, there is a temptation to cut the advanced premaxilla loose from the vomer and carry it back between the lateral walls of the cleft and facilitate closure of the lip. This procedure frequently results in undue flatness of the upper lip, atrophy of the premaxilla, permanent nonunion, and backward position of the upper anterior teeth when they erupt. It is much better not to disturb the protruded premaxilla at this time, but to close the lip cleft over it, and

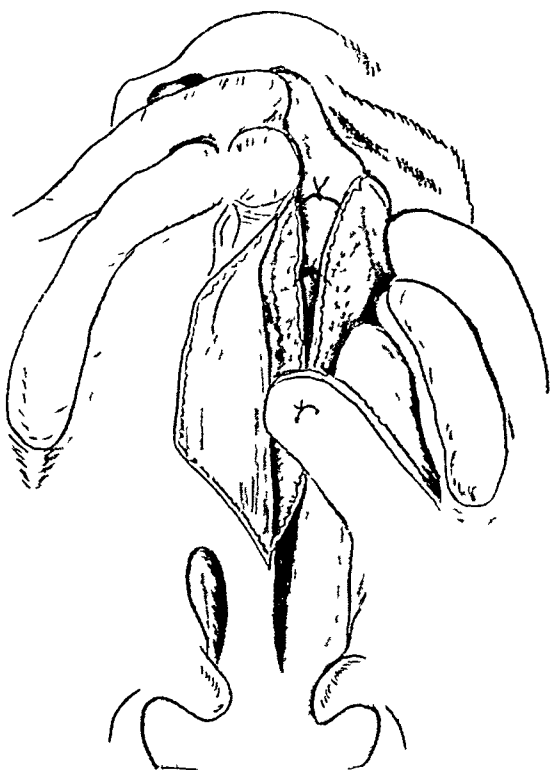


FIG 9—Nasal mucosa freed anteriorly and sutured to front of vomer flap to close cleft under lip (After Veau)

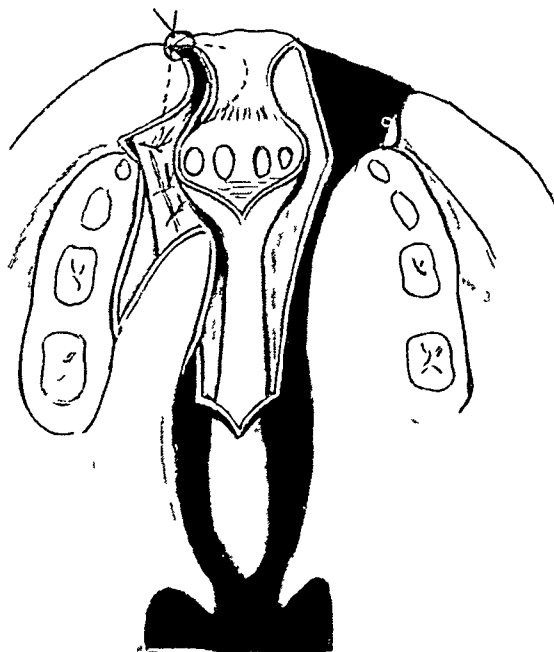


FIG 10—Closure of anterior part of bilateral cleft on one side by vomeropalatal flap technique converting bilateral into unilateral cleft. The other side is closed a few weeks later (After Veau)

if this does not suffice to gradually bring it into correct position, a later operation can be done for this purpose. In these bilateral cases the same principle is followed as for the unilateral cases, except that one side is operated on at a time, the bilateral cleft being first converted into a unilateral one. The vomer mucosa is split longitudinally and a flap turned over on one side, to be sutured beneath a mucoperiosteal flap raised on one side of the hard palate. The corresponding side of the lip is closed at the same sitting (Fig 10). A few weeks later the opposite side of the cleft is closed in a similar manner. The case is completed by closure of the posterior part of the cleft by the Axhausen technique at two and one-half to three years of age.

(3) *Median Cleft of Soft Palate Usually Extending a Varying Distance into the Hard Palate*—Cases of this group may vary from a split in the uvula and soft palate alone, to involvement of the hard palate right up to the pre-

maxilla These clefts are always in the midline and the lower edge of the vomer may be free They vary very greatly not only in length but also in width, and may present great difficulty in successful closure Velopharyngeal insufficiency is more common in this type of cleft than in the other types Many operators advocate closure of these clefts at an early age, varying from six to 18 months, on the plea that speech will be better if the cleft is closed before the child begins to talk We do not believe that the chances for good speech results are materially impaired by waiting until two and one-half to four years of age before closure of the posterior cleft At the later age the mortality will be lower and the chances of good anatomic closure much better During the past three years we have employed the Axhausen technic, already described, for closure of this type of cleft

A summary of the age at time of operation and the procedure employed is shown below

APPROXIMATE AGE AND PROCEDURE RECOMMENDED FOR TREATMENT OF
VARIOUS FORMS OF CLEFT LIP AND PALATE

(1) *Complete Unilateral Cleft of Hard and Soft Palate*

(a) Six weeks to three months—Veau turnover flap from vomer to close anterior part of hard palate, followed at same sitting by closure of lip cleft by Blair-Mirault procedure

(b) Two and one-half to three years—Axhausen operation for remaining cleft in hard and soft palate

(2) *Complete Bilateral Cleft of Hard and Soft Palate*

(a) Six weeks to three months—Veau turnover flap from vomer to close anterior part of hard palate on one side, followed at same sitting by closure of lip on same side by Blair-Mirault procedure, converting bilateral into unilateral cleft Followed about four weeks later, by same procedure on opposite side In most cases the protruding premaxilla gradually assumes correct position by pressure of closed lip

(b) Two and one-half to three years—Axhausen operation for closure of remaining cleft in hard and soft palate

(3) *Median Cleft of Soft Palate Usually Extending a Varying Distance into the Hard Palate*

Two and one-half to three years—Axhausen operation

(4) *Cases of Velopharyngeal Insufficiency*

For cases of cleft palate, where the usual operations would not provide sufficient tissue posteriorly to permit velopharyngeal closure, excellent speech results may be obtained by the "push-back" operation of Dorrance, usually performed in two stages, not earlier than four years of age This operation is also recommended as a secondary procedure where other methods have given inadequate velopharyngeal closure The modification published by Barrett Brown^{3, 4} permits a one-stage procedure with safety

Cases treated during the past three years, since we have employed the above-described technic, on the author's service at the Presbyterian, Graduate

and University Hospitals, in association with Dr Lawrence Curtis and Dr Henry A Miller, may be grouped as follows

(Results are recorded as Good, in which no secondary operations were necessary, Fair, in which an opening remained, requiring secondary operation for closure, Failure, in which the operation was completely unsuccessful)

(1) Complete Unilateral Cleft Palate, in which the Veau-Axhausen Sequence Was Followed

Number of Cases	—Result—	
	Good	Fair
27	21	6

(2) Complete Bilateral Cleft Palate, in which the Veau-Axhausen Sequence Was Followed

Number of Cases	—Result—	
	Good	Fair
9	8	1

(3) Median Cleft, in Which the Axhausen Operation Was Performed

Number of Cases	—Result—	
	Good	Fair
21	12	9

(4) Cases of Velopharyngeal Insufficiency, in Which the "Push-Back" Operation Was Performed

(a) Primary Cases

Number of Cases	———Result———		
	Good	Fair	Failure
15	11	2	2

(b) Secondary Cases

Number of Cases	—Result—	
	Good	Fair
5	4	1

Total No of Finished Cases	———Result———		
	Good	Fair	Failure
77	56	19	2

(5) Unfinished Cases, in Which Only the First-State Veau Operation has, So Far, Been Performed

	Number of Cases	———Result———		
		Good	Fair	Failure
(a) Unilateral	18	16	1	1 (death)
(b) Bilateral	8	7	1	
	—	—	—	—
Total	26	23	2	1

In addition to these, there were 53 cases in which miscellaneous secondary operations were undertaken in order to improve results in cases primarily operated upon elsewhere

The results so far obtained in this series of cases encourage us to continue with the procedures described above, as a routine in typical cases of cleft palate

I am indebted to Dr Henry A Miller for looking up the records of the cases

REFERENCES

- ¹ Axhausen, G *Technic and Results of Cleft Palate Surgery* Leipzig, Thieme, 1936
- ² Blair, V P, and Brown, J B *Surg, Gynec and Obstet*, 51, 81, 1930

- ³ Brown, J B Surg, Gynec and Obstet, 63, 768, 1936
- ⁴ Brown, J B Surg, Gynec and Obstet, 70, 815, 1940
- ⁵ Dorrance, G M The Operative Story of Cleft Palate Philadelphia, W B Saunders, Co, 1933
- ⁶ Ivy, R H, and Curtis, L ANNALS OF SURGERY, 100, 502, 1934
- ⁷ Ivy, R H Internat Abst Surg, 64, 433, 1937
- ⁸ Veau, V La Division Palatine, Paris, Masson et Cie, 1931

THE USE OF INTRAMUSCULAR INJECTIONS OF 2-METHYL-1, 4-NAPHTHOQUINONE IN THE TREATMENT OF PROTHROMBIN DEFICIENCIES*

WITH A NOTE ON THE RÔLE OF THE LIVER IN THE RESPONSE TO THIS AND OTHER SUBSTANCES WITH VITAMIN K ACTIVITY

WILLIAM DEWITT ANDRUS, M D , AND JERE W LORD, JR , M D
NEW YORK, N Y

FROM THE DEPARTMENT OF SURGERY OF THE NEW YORK HOSPITAL AND CORNELL UNIVERSITY MEDICAL COLLEGE, NEW YORK, N Y

THE DEMONSTRATION of a deficiency in the prothrombin activity of the plasma as the responsible factor in the hemorrhagic tendency sometimes occurring in obstructive jaundice and hemorrhagic disease of the newborn, and the experimental and clinical evidence which has accumulated during the past few years indicating the vital rôle played by the accessory food factor known as vitamin K in the production of prothrombin, have, logically, stimulated the purification and identification of the vitamin. It, apparently, occurs in at least two forms which have been identified by MacCoiquodale, Binkley, Thayer and Doisy,¹ and by Fieser and his coworkers.² Almquist and Klose³ had previously shown that phthiocol (2-methyl-3-hydroxy-1, 4-naphthoquinone) possessed vitamin K activity, and a large number of other naphthoquinones have since been investigated. Of all those tested, however, it has become evident that only the 1, 4-naphthoquinones have this property, and of these, by far the most potent is synthetic 2-methyl-1, 4-naphthoquinone. These substances have now largely supplanted the cruder extracts formerly used, and while there is some difference of opinion as to the potency of 2-methyl-1, 4-naphthoquinone as compared to the crystalline vitamin, most workers are in agreement that its effectiveness is at least equal to, or even surpasses, that of the vitamin itself. This fact, together with the ease with which it can be synthesized, makes 2-methyl-1, 4-naphthoquinone the best available agent for the correction of prothrombin deficiencies.

It has been successfully employed in a number of clinics, and can be administered orally,^{4, 5} intramuscularly^{6, 7} or intravenously. For intramuscular injection, the crystalline substance is dissolved in corn oil and for intravenous use, either 2-methyl-1, 4-naphthoquinone 1 mg in 10 cc of distilled water or a more soluble derivative may be employed. We believe the intramuscular route to be the simplest and most effective, since there is no reaction at the site of injection and the effect is evident within a few hours.

Presented by Title before the American Surgical Association, St. Louis, Mo., May 1, 2, 3, 1940.

* This study was carried out under a grant from the John and Mary R. Markle Foundation.

Its action is also, definitely, more prolonged than when the substance is given orally. Thus, a single injection of 2 mg has elevated the prothrombin of patients by as much as 40 per cent, and in one individual, 11 days elapsed before it again fell. Tage-Hansen⁸ noted similarly prolonged effects when large doses of purified vitamin K were injected intramuscularly. Further points in favor of the parenteral route are certainty of absorption and the lack of need for the coincident administration of bile salts which are not always well tolerated.

Since October 1, 1939, we have administered 2-methyl-1, 4-naphthoquinone, intramuscularly, to 49 patients with initial plasma prothrombin levels of from 5 to 80 per cent of normal by the test of Warner, Brinkhous and Smith.⁹ Doses of 2 mg were employed routinely—except in infants who received from 0.35 to 1 mg—and with uniformly good results in the absence of severe liver damage. In many instances, a single injection of 2 mg sufficed to restore the plasma prothrombin to a satisfactory level, and, in most, the higher level was maintained for from several days to a week or even longer, but in some the injection was repeated at two- or three-day intervals. Daily injections of the same, or even twice the amount for two to four days, were employed in those cases in which the presence of severe liver damage made the response less likely to be satisfactory. The types of cases in which this therapy was employed and the response in percentage of the normal level obtained to a single injection of 2-methyl-1, 4-naphthoquinone are shown in Table I.

TABLE I

Diagnosis	No of Cases	Response in Percentage of Normal
Obstructive jaundice due to stone	12	4-48
Obstructive jaundice due to stricture	1	11
Carcinoma of head of pancreas	4	10-40
Catarrhal jaundice	2	1-6
Cirrhosis of the liver	5	Continued to fall
Liver abscesses with empyema	1	12
Liver abscesses— <i>Cl welchii</i>	1	0
Cholelithiasis	1	33
Hemorrhagic disease of newborn	10	5-30
Carcinoma of stomach	3	10-20
Peptic ulcer	1	28
Faulty gastro-intestinal absorption	2	28-29
Repeated gastro-intestinal hemorrhage—unknown origin	1	18
Idiopathic purpura	1	38
Thrombasthenia	1	28
Empyema, sepsis	1	35
Nephrosis with septicemia	1	47
Endocrine imbalance	1	12
Total	49	

In view of the mass of accumulated clinical evidence that liver damage interferes with the response to substances with vitamin K activity, it is important to consider the normal rôle of the liver in the metabolism of vitamin K and the production of prothrombin. The available evidence indicates that this organ, aside from the production of bile salts which are necessary in the absorption of the vitamin from the intestinal tract, is a storehouse of the vitamin itself. Thus, after its absorption, the vitamin is stored in the liver, probably in a somewhat altered form,¹⁰ and this reserve is gradually depleted when, for any reason, continuous absorption from the intestinal tract is interfered with. Concomitant with the disappearance of the vitamin from the liver, the level of the plasma prothrombin falls¹⁰ and the hemorrhagic tendency becomes evident when it reaches a certain critical level. Thus, an animal or patient may develop a prothrombin deficiency without liver damage after a time, when the vitamin is no longer absorbed from the intestinal tract due to absence of bile, as in obstructive jaundice or biliary fistula, or in certain cases of severe enterocolitis. When the vitamin is supplied, however, prompt restoration of the plasma prothrombin follows in these cases.

Experimental evidence also indicates that the prothrombin normally disappears from the plasma at a fairly rapid rate, so that any interference with its production will be soon followed by a drop in the plasma prothrombin level. The site of its disappearance appears to be in the lungs, as it has been shown¹¹ that there is an appreciable difference in the level of the plasma prothrombin in blood from the right and left sides of the heart.

The effect of liver damage on the plasma prothrombin level has been demonstrated experimentally by a number of workers. Thus, Smith, Warner and Brinkhous¹² noted a fall in the plasma prothrombin level to less than 5 per cent of normal after 90 minutes of chloroform anesthesia. Lord¹³ found that gentle massage of the liver was followed by a depression of the prothrombin level amounting to 25 per cent, a possible contributing factor in hemorrhage in jaundiced patients after operation. Warner¹⁴ showed that removal of 65 per cent of the liver in rats also caused a fall which was recovered from in about two and one-half weeks. Warren and Rhoads,¹⁵ and Andrus, Lord and Moore,¹⁶ independently, found that complete hepatectomy in dogs caused the plasma prothrombin to fall to below 10 per cent of normal within 14 hours, and the latter authors demonstrated that the administration of 10,000 units of vitamin K and bile salts into the intestinal tract failed to prevent this drop. We have since repeated this work, using as much as 80,000 units of 2-methyl-1, 4-naphthoquinone intramuscularly and intravenously, without affecting the curve of fall of the plasma prothrombin after hepatectomy.

The failure of patients with varying degrees of liver damage to respond adequately, or at all, to the administration of substances with vitamin K activity, has been widely noted by clinicians. Thus, Quick,¹⁷ Butt, Snell and Osterberg,¹⁸ and others^{19, 20, 21} reported cases in which poor response was obtained and attributed this to liver damage. In December, 1938, we observed

a case which strikingly demonstrated the effect of liver damage on the utilization of vitamin K. The patient, female, age 50, was admitted with jaundice due to stone in the common duct and acute cholecystitis. The plasma prothrombin was only 25 per cent on admission, but rose very satisfactorily to normal during the next four days on the administration of Cerophyl and bile salts. Despite the continued administration of the vitamin, however, the patient's prothrombin then fell precipitously and remained below 30 per cent thereafter. At postmortem, the liver showed the following

Case 1—E. B. New York Hosp No 221902. Massive liver necrosis, secondary to thrombosis of the hepatic artery and the portal vein.

Pathologic Examination—*Gross*. The liver together with the duodenum and pancreas weighs 2,350 Gm. The surface is nodular and mottled red, bluish-purple and yellow. On section, the peripheral 6 cm is dark, cystic, mottled green, yellow and dark red. It is crepitant. There are numerous similar areas scattered throughout the inner portion, the normal architecture of which is preserved but much bile-stained. An approximate two-thirds to three-quarters of the parenchyma is necrotic. The bile ducts contain in many cases a brown, firm material. Numerous intrahepatic branches of the portal vein contain firm, brown material. There is a large organizing thrombus, approximately 5 cm in length, in the portal vein before it branches. There is a 2 cm firm, friable thrombus attached to the wall of the hepatic artery 4 cm below its branching.

Microscopic. The cords are broken and fragmented. The cells are swollen and granular. This is especially conspicuous in the central portions of the lobule where throughout the section the sinusoids are large and filled with pink, granular material, erythrocytes and a few polymorphonuclear leukocytes. The liver cells in these areas are ill-defined, and contain much brown pigment. The biliary canaliculi are engorged with brown material. This is more advanced in some areas than others. The periportal tissue is slightly increased and infiltrated with lymphocytes. Many of the bile ducts in these spaces are distended with brown material. Clumps of granular, blue substance are scattered throughout the section, indiscriminately. There are a few hemorrhages. Throughout all the sections are large areas where the normal architecture is lost, the liver cords fragmented and the necrotic cells separated by large and small spaces, some of which contain pink, granular material. In one section is a vessel in which there is an organized thrombus.

In the earlier cases, the possibility that the vitamin might have been poorly absorbed threw some doubt on the implication of the liver in the poor response although in this case the primary response was excellent, but since the highly potent 2-methyl-1, 4-naphthoquinone has been available, and similar failures have followed its parenteral administration, the connection between liver damage and inadequate restoration of prothrombin levels after the administration of the vitamin would seem to be established.

Since our experience with the case mentioned above, we have encountered nine additional patients with lowered plasma prothrombin levels who failed to respond to even relatively large doses of substances with vitamin K activity. Eight were treated with intramuscular injections of 2-methyl-1, 4-naphthoquinone and one received Klotogen and bile salts by mouth. Three of these patients have clinical evidence of liver damage as indicated by liver function tests, and in the remaining six, it has been possible to study the liver either at operation (two cases) or at postmortem. All showed pathologic changes

of severe grade, but the types of lesions encountered were so diverse as to shed little light on the exact condition responsible for the decreased prothrombin production. The pathologic descriptions of the liver in these cases were as follows:

Case 2—A. G. New York Hosp. No. 241700. Periportal cirrhosis, cholangitis.

Pathologic Examination—Gross The liver weighs 2,070 Gm. The surface is roughened by nodules measuring up to 2 Mm. across. The organ is dark green-brown. On section, the normal lobular architecture is replaced by a nodular architecture. These nodules are for the most part small and measure up to 3 Mm. across and are separated from one another by dense gray-white fibrillar tissue. These nodules vary in color from green to dark brown. The intrahepatic portal spaces visible show no changes. The organ is increased in consistency.

Microscopic The capsule is slightly thickened and infiltrated with lymphocytes. The normal lobular architecture of the liver is distorted by fragmentation of the liver cords, by eccentricity of the central veins, and by conspicuous increase in the periportal connective tissue. The cytoplasm of the individual liver cells is granular, acidophilic, and contains brown pigment granules. The cords are fragmented and widely separated by sinusoids distended with blood and by fibrous tissue. The sinusoidal epithelium is separated from the cords of liver cells by small amounts of pink, granular material. In a small number of places through the section the bile canaliculi are distended by inspissated bile. The periportal spaces and lobules are infiltrated by large numbers of lymphocytes and polymorphonuclear leukocytes. Proliferating bile ducts in these areas are numerous. Many bile ducts have polymorphonuclear leukocytes in the lumen and in the epithelium.

Case 3—J. P. D. New York Hosp. No. 256206. Cirrhosis with central necrosis.

Pathologic Examination—Gross The liver is slightly enlarged, weighing 2,200 Gm. It is yellow-gray in color, and moderately firm. The capsule appears thickened and the surface is finely nodular. On section, the substance appears to be made up of many small nodules of hepatic tissue up to 3 Mm. in diameter, embedded in a moderately dense fibrous stroma. No definite areas of necrosis are seen.

Microscopic Thick bands of connective tissue, moderately infiltrated with round cells, separate the liver substance into irregular lobules of various sizes. In many of the fibrous regions are seen numerous small bile ducts. The hepatic cells, generally, show no changes at the periphery of lobules, but in the central portions are wide areas of recent necrosis, probably involving one-fourth of the hepatic cells in the section. In the more normal hepatic cells the canaliculi contain bile pigment.

Case 4—T. H. New York Hosp. No. 256106. Pylephlebitis with multiple liver abscesses.

Pathologic Examination—Gross The liver weighs approximately 3,000 Gm., it is pale, soft and friable. There is fibrinopurulent exudate over many parts of the liver and it is most conspicuous in the inferior lateral part. Above, the liver is adherent to the diaphragm. The cut-surface of the right lobe of the liver is studded with many abscesses that vary from a few millimeters up to 7 cm. across. A few of them are lined with a pyogenic membrane and are filled with a thick, creamy, odorless pus. Others are not so well circumscribed and contain bile. The largest abscesses are in the inferior-posterior part of the liver. There are a few smaller abscesses in the left lobe. The portal vein is filled with an infected thrombus that extends along the splenic and superior mesenteric veins for a considerable distance. The gallbladder is of normal size, is edematous and the mucosa is injected. The bile contains a considerable amount of purulent material. The ducts are patent.

Microscopic The capsule is thick and covered in one area with a necrotic fibrinous exudate. There are several circumscribed abscesses throughout the section some of which

are composed predominately of monocytes and necrotic liver tissue. These abscesses have undergone complete necrosis. There are bile thrombi in several of the bile ducts.

Case 5—G. G. New York Hosp No 258992. Multiple liver abscesses with widespread gas bacillus infection.

Pathologic Examination—*Gross*. The liver weighs approximately 250 Gm. It is intimately adherent to the stomach and the granulating wound of the anterior abdominal wall. A sinus tract in the center of the large granulating wound of the anterior abdominal wall can be probed to a depth of 9 or 10 cm and is in communication with the interior of the liver. The external surface of the liver is brown in color and is mottled by lighter brown areas in the usual way. There is an incision 3 cm in length on the anterior surface of the liver. This extends 1 cm into the liver substance. A number of fine fibrinous adhesions roughen the external capsular surface. The liver is fluctuant and, on section of the right lobe, a large amount (approximately 200 cc) of very foul, green, purulent material escapes. Cuts made in other portions of the liver reveal similar changes throughout the entire organ, replacing approximately 60 to 70 per cent of the liver substance. In the left lobe of the liver is a large area with a honeycomb-like structure. The borders are composed of light brown tissue, arranged in a circinate manner. The liver tissue, outside of these areas of frank abscess formation, is apparently well preserved and has the usual architectural pattern. Cultures of the pus yielded *Cl. welchii* and streptococci.

Microscopic. The first section was taken from an area of abscess formation, and is made up largely of polymorphonuclear leukocytes, necrotic liver cells and clusters of bacteria. Between the abscesses there is, however, a surprising amount of good liver tissue remaining. The portal areas are infiltrated extensively by inflammatory cells. The chief cells are lymphocytes, but there are a large number of plasma cells and polymorphonuclear leukocytes. Careful study of cross-sections of the bile ducts fails to reveal any inflammatory exudate within them. The sinusoids between the liver cords are widely dilated and contain large numbers of polymorphonuclear leukocytes as well as considerable cellular debris. The liver cells contain large quantities of bile pigment. One small vein contains a thrombus made up of polymorphonuclear leukocytes, platelets and fibrin.

The second section of liver was taken from the periphery of the organ, away from the areas of massive abscess formation. The capsule is moderately thickened and infiltrated by inflammatory cells. These are chiefly lymphocytic in type. There is dilatation of the lymphoid spaces, within and beneath the capsule. There is marked increase in fibrous tissue in some of the portal areas which are infiltrated by similar inflammatory cells. The sinusoids are dilated and infiltrated by numerous polymorphonuclear leukocytes. This is most conspicuous in the central portion of the lobules. The cells within the central portions of the lobules contain large quantities of bile pigment.

Case 6—C. M. New York Hosp No 226577. Subacute periportal hepatitis.

Surgical pathologic report on biopsy taken at operation.

Pathologic Examination—*Gross*. Specimen consists of a small wedge of dark red liver tissue, measuring 6x4x3 Mm. It is in no way grossly remarkable except that it is very firm.

Microscopic. There is destruction of the normal architecture of the liver by the periportal inflammation. Many liver cells have undergone fatty degeneration. Surrounding the blood vessels and bile ducts, in the periportal areas, there is evidence of hemorrhage and proliferation of fibrous tissue. Bile pigment deposits are present in these areas and an infiltration with polymorphonuclear leukocytes and monocyctic cells.

Case 7—P. L. New York Hosp No 255971. Laennec's cirrhosis.

Description of the operative pathology of the liver. "The liver was found to be extremely small, perhaps less than half its normal size, discolored and dark brownish in color, finely nodular, and everywhere very firm, presenting the picture of a very advanced cirrhosis. The liver edge lay about 6 cm above the costal margin."

SUMMARY

(1) Forty-nine patients with levels of plasma prothrombin activity between 5 and 80 per cent of normal, by the test of Warner, Brinkhous and Smith, have been treated by means of intramuscular injections of 2-methyl-1, 4-naphthoquinone with very satisfactory response in 41

(2) In three of these 49 patients, there was clinical evidence of liver damage, as indicated by liver function tests, but its exact nature is not yet known. In the five others, who failed to respond to 2-methyl-1, 4-naphthoquinone, and in two additional cases, not included in the above series, who were treated with Cerophyl or Klotogen but whose prothrombin did not rise despite continued administration of the vitamin, the presence of marked liver damage was definitely proved—at operation in two cases or at postmortem examination in five cases

(3) These seven patients presented a wide variety of pathologic pictures, including Laennec's cirrhosis, cholangitis, periportal hepatitis, multiple liver abscesses complicating pylephlebitis, gas bacillus infection, cirrhosis with central necrosis, and massive infarction of the liver secondary to thrombosis of the hepatic artery and portal vein

(4) These lesions were so diverse in nature and so widespread in extent as to yield little information regarding any specific type of liver injury responsible for the decreased prothrombin production

BIBLIOGRAPHY

- ¹ MacCorquodale, D W, Binkley, S B, Thayer, S A, and Doisy, E A On the Constitution of Vitamin K Jour Am Chem Soc, 61, 1928, 1939
- ² Fieser, L F, *et al* Quinones Having Vitamin K Activity Jour Am Chem Soc, 61, 1925, 1939
- ³ Almquist, H J, and Klose, A A The Antihemorrhagic Activity of Certain Naphthoquinones Jour Am Chem Soc, 61, 1923, 1939
- ⁴ Koller, F Uber die klinische Wirksamkeit von Naphtochinonderivativen (Vitamin K—Wirkung) Schweiz med Wchnschr, 69, 1159, 1939
- ⁵ Rhoads, J E, and Fliegelman, M T The Use of a 2-Methyl-1, 4-Naphthoquinone (a Synthetic Vitamin K Substitute), in the Treatment of Prothrombin Deficiency in Patients J A M A, 114, 400, 1940
- ⁶ Macfie, J A, Bacharach, A L, and Chance, M R A The Vitamin K Activity of 2-Methyl-1, 4-Naphthoquinone and Its Clinical Use in Obstructive Jaundice Brit Med Jour, 2, 1220, 1939
- ⁷ Andrus, W DeW, and Lord, J W, Jr Correction of Prothrombin Deficiencies by Means of 2-Methyl-1, 4-Naphthoquinone Injected Intramuscularly J A M A, 114, 1336, 1940
- ⁸ Tage-Hansen, Erik Summary of Some Clinical Studies on Vitamin K J A M A, 113, 1875, 1939
- ⁹ Warner, E D, Brinkhous, K M, and Smith, H P Quantitative Study on Blood Clotting Prothrombin Fluctuations Under Experimental Conditions Am Jour Physiol, 114, 667, 1936
- ¹⁰ Lord, J W, Jr, Andrus, W DeW, and Moore, R A Studies on the Metabolism of Vitamin K and on the Rôle of the Liver in the Production of Prothrombin in Animals Arch Surg, in press

- ¹¹ Andrus, W DeW, Lord, J W, Jr, and Kauer, J T Studies on the Fate of Plasma Prothrombin Science, **91**, 48, 1940
- ¹² Smith, H P, Warner, E D, and Brinkhous, K M Prothrombin Deficiency and Bleeding Tendency in Liver Injury (Chloroform Intoxication) Jour Exper Med, **66**, 801, 1937
- ¹³ Lord, J W, Jr Effect of Trauma to Liver on Plasma Prothrombin Experimental Study Surgery, **6**, 896, 1939
- ¹⁴ Warner, E D Plasma Prothrombin Effect of Partial Hepatectomy Jour Exper Med, **68**, 831, 1938
- ¹⁵ Warren, R, and Rhoads, J E The Hepatic Origin of the Plasma Prothrombin Observations after Total Hepatectomy in the Dog Am Jour Med Sci, **198**, 193, 1939
- ¹⁶ Andrus, W DeW, Lord, J W, Jr, and Moore, R A The Effect of Hepatectomy on the Plasma Prothrombin and the Utilization of Vitamin K Surgery, **6**, 899, 1939
- ¹⁷ Quick, A J The Nature of the Bleeding in Jaundice J A M A, **110**, 1658, 1938
- ¹⁸ Butt, H R, Snell, A M, and Osterberg, A E The Preoperative and Postoperative Administration of Vitamin K to Patients Having Jaundice J A M A, **113**, 383 1939
- ¹⁹ Brinkhous, K M, Smith, H P, and Warner, E D Prothrombin Deficiency and the Bleeding Tendency in Obstructive Jaundice and in Biliary Fistula Effect of Feeding Bile and Alfalfa (Vitamin K) Am Jour Med Sci, **196**, 50, 1938
- ²⁰ Stewart, J D, and Rourke, G M Prothrombin and Vitamin K Therapy New England Jour Med, **221**, 403, 1939
- ²¹ Illingworth, C F W Hemorrhage in Jaundice Lancet, **1**, 1031, 1939

FURTHER ANESTHESIA STUDIES WITH PHOTO-ELECTRIC OXYHEMOGLOBINOGRAPH*

FRANK W HARTMAN, M D AND ROY D McCLURE, M D
DETROIT, MICH

THE DATA we wish to present are a continuation of studies on anoxia in surgery, presented to the Association last year. Those studies on experimental animals and surgical patients were made through the application of Warburg's method for tissue respiration and Van Slyke's manometric method for oxygen saturation of the arterial blood. Both of these methods are not only slow and laborious but, at best, can be applied only at intervals.

During the course of this earlier work the necessity for continuous observations of the oxygen saturation became apparent, and the work of Kurt Kramer and Karl Matthes, published in 1934 and 1935, was reviewed. Both investigators measured the oxygen saturation of the blood by means of light absorption as determined with photo-electric cells and galvanometers. This work was fundamental, as seen in the following excerpts from their papers. Kramer, 1934 "For the study of metabolic-physiologic problems a method was needed which would permit the easy determination of the oxygen content of the blood at short intervals or even continuously in the animal body. This requirement was not met by any of the methods thus far used, including the manometric determination of Van Slyke and the improved spectral analytic determination of Routon and Hartridge. The development of the photo-electric cell technic, especially Lange's barrier layer cells, made it possible to utilize the spectral peculiarities of hemoglobin to carry out oxyhemoglobin determinations *in vitro* and, perhaps, *in vivo* quickly and accurately." Through these investigations Kramer confirmed the validity of Beer's law for hemoglobin solutions.

Based on the original observations, the second paper, of 1935, reported a method for the continuous oxygen analysis of the blood in closed vessels of an animal with accuracy to 1 per cent saturation. In explanation, Kramer stated "It has been demonstrated that the light absorption of hemoglobin solutions even in high concentrations, is subject to Beer's laws. It, therefore, could be assumed that the condition of the hemoglobin molecule of the normal blood which is found in the erythrocyte, in 30 per cent concentration, would not greatly complicate the laws of light absorption. Therefore, the light permeability of the hemoglobin, which varies with the oxygen content, had to be fundamentally similar to the photo-electric findings in pure hemoglobin solutions. The principle of the method is based on the spectral differences of the hemoglobin and oxyhemoglobin in the red wave length section."

* Read before the American Surgical Association, St. Louis, Mo., May 1, 2, 3, 1940

Karl Matthes, 1934 "Since the fluctuations of the filling of the pulmonary reservoir are changing rapidly, the analysis of blood samples obtained by puncture permitted only a very inadequate picture of the entire process. We, therefore, searched for a method for continued recording of the oxygen content of the blood in arteries and veins. Such a possibility was presented by the well-known differences in the light absorption of oxyhemoglobin and reduced hemoglobin. After the technical part of these investigations had been completed, Kramer published a method very similar in principle." Matthes used mercury vapor lamp after Nicolai. Kramer used ordinary light with Zeiss-red filter R G I—"A method has been evolved which permits the continuous optical registration of the oxygen content and the total concentration of the hemoglobin in the blood of a given vessel, instead of periodic withdrawal of blood which is subject to many technical disadvantages."

"The principle of the new technic which employs photo-electric methods consists in the registration of the absorption of light of two spectral regions through the blood." Under the title "Investigation of the Oxygen Saturation of Human Arterial Blood," Matthes, in 1935, applied the red-sensitive photocell used by Kramer to the ear lobe after histamine iontophoresis. In conjunction, in order to evaluate the passive fluctuations of the vascular bed, a plethysmogram of the other histaminized ear lobe was made. These simultaneous records allowed the immediate recognition and the elimination of all distortions of the oxygen saturation curve caused by changes of the blood content of the ear lobe. The oxygen saturation curve was calibrated by blood determinations during oxygen, air and 88 per cent nitrogen respiration. During the first, the saturation was found always to be 100 per cent.

From this analysis of the work of Kramer and Matthes it seems demonstrated that measurement of light absorption by red-sensitive photo-electric cells is capable of giving accurate oxygen saturation values for hemoglobin *in vivo*, in blood vessels or in selected skin areas providing other variables, especially the total hemoglobin in the circulation and the volume of the part within the cell, are taken into consideration. The first of these variables is of secondary importance since large enough changes in the total hemoglobin occur only after adrenalin to materially alter the oxygen saturation values. The second of the variables, that is volume of the part, should be recorded in parallel as it was by Matthes. Kramer dealt with large vessels, filling his rigid cells, thus avoiding this factor. Matthes histaminized the ear lobe used and generally obtained plethysmographic records of the other ear lobe using a combination volume and photo-electric cell method. In 1937 and 1938, Hertzman, of St. Louis University, described the use of a photo-electric plethysmograph, for studying the blood supply of various skin areas. This apparatus resembles that of Kramer and Matthes except that a photo-electric cell of the photo-emissive type rather than the red-sensitive or the green-sensitive type was used. Hertzman mentions the influence of reduced

hemoglobin-oxygenated hemoglobin ratio on skin opacity, but his detailed observations apparently have not been published

SUMMARY

(1) In our work, thus far, volume changes of the parts incorporated in the photo-electric cell have not been recorded in parallel, but with the increasing stability and dependability of the machine, volume changes are to be included in these studies

(2) Volume has been controlled to some extent by heating the area studied through the photo-electric cell and by bringing the light and cell outlets snugly against the skin

(3) As a guide for the surgeon during anesthesia, low oxygen saturation of the arterial blood and increased volume in the capillary bed are equally significant danger signals, hence if light absorption increases sharply due to one or the other, or both, corrective measures are indicated

(4) If the respirations are of usual rate and amplitude, oxygen should rapidly reduce the high light absorption. Lack of response to oxygen suggests a dilated capillary bed and low blood pressure

DISCUSSION—DR ROY D. McCLURE (Detroit, Mich.) We are inclined to believe that not enough attention is paid to anoxia during anesthesia. In recent years, there have been reported occasional deaths on the operating table during anesthesia. Autopsies have been obtained on these patients and the typical changes of anoxia have been demonstrated. Our attention has also been drawn to several patients in whom mental and physical derangements occurred after anesthesia. It is our opinion that these changes have been produced by anoxia.

We have one patient that I should like to report. A young lady led her class in her particular section of the first year's work. She came to Detroit one morning and had a tooth extracted under nitrous oxide. On returning to her home that afternoon she noticed that her vision was blurred, but neither she nor her parents associated this change with the pulling of the tooth. Later she consulted an oculist who tested her eyes and gave her glasses. On her return to school she noticed no further change in herself, but when the next term examinations came up she made very bad marks, and before the year was out she failed in her work. On the next visit to this dentist, a year later, for another impacted molar on the opposite side, he said to her "For heaven's sake, don't let anybody ever give you gas again because you just can't take it." It then came out that during her first anesthesia, which was a gas anesthetic, she had become blue and had to be given artificial respiration.

In discussion of this subject with different groups of doctors there are always some who have noticed changes in a patient after anesthesia. We feel that the exact nature of these changes, despite their importance, is often not recognized and that undoubtedly many more cases of slight anoxia with permanent damage occur than is commonly suspected. I do not know how we can detect this condition except, perhaps, by earlier mental tests of patients such as this particular girl had in her school, because such changes were not even recognized by her family.

We have been attempting to study this problem of anoxia by making arterial punctures and estimating the oxygen content of the blood during anesthesia. This method is cumbersome and requires too much time to be of practical value. It is obvious that a method of such blood analysis must be immediate, and the search for some such practical method is responsible for the report given here to-day by Doctor Hartman. This method with the electric eye is immediate and striking, and we hope may soon prove to be of considerable practical importance.

MEMOIRS

GEORGE EMERSON BREWER

1861-1939

GEORGE BREWER'S first appearance before the American Surgical Association was when he was asked to take part in a symposium on gallbladder disease, in 1899. His paper was on the "Diagnosis of the Diseases of the Gallbladder and Ducts." The other contributors were Hans Kell, of Halberstadt, Halsted and W. J. Mayo. The following year he was elected to membership and attended all the meetings of the Association until his retirement, in 1927, except for the years of his overseas service. During this long membership he took an active part in the proceedings and was elected president in 1920.

He was born at Westfield, N. Y., July 28, 1861, the son of Francis B. Brewer and Susan H. Rood. On June 29, 1893, he married Effie Leighton Brown, at Chester, Pa., there being two children, Leighton and George Emerson, Jr.

In his later years as teacher, as diagnostician, and in his care of his patients he showed the effects of his broad early training. While at Hamilton College, where he received the degrees of A. B., in 1881, and A. M., in 1884, he was the college organist. His first two years of medical study were spent at the University of Buffalo. During this period he lived with Dr. Julius F. Minor, Professor of Surgery, and assisted him with his operations and in his office. During these summers, he acted as apothecary at the State Insane Asylum. He entered the third-year class at Harvard University, and received his M. D. degree in 1884. Before graduation, he won first place in the intern examinations for the Boston City Hospital, where he served with Drs. Robert Lovett, John Munro and Leonard Wood. After a residency in obstetrics and gynecology at Columbia Hospital for Women, in Washington, D. C., in 1886, he went to Baltimore as "fellow by courtesy" at Johns Hopkins University, under Dr. William H. Welch. He also held a position at this time as Resident Superintendent of the Baltimore City Insane Hospital.

In 1887, he came to New York and started the general practice of medicine, working in the Out-Patient departments of Roosevelt, Bellevue and Chambers Street Hospitals. The following year, he became the assistant of Dr. Henry Holbrook Curtis, an eminent nose and throat specialist, an association that lasted five years. During these summers, he carried on an active general practice at Block Island.

His first appointment to the College of Physicians and Surgeons, Columbia University, was that of assistant in Genito-Urinary Surgery to Dr. Fessenden Nott Otis. In 1892, he became assistant demonstrator of anatomy, and during that summer studied in Edinburgh under Sir William Turner and Doctor

Hepburn He was appointed attending surgeon at the City Hospital in 1899. It was here that he began his studies in operating room technic, which were of great influence in that important period of surgery. Two years later, he was



4.11.1906
Geo. H. B.
NY

GEORGE EMERSON BREWER

made junior surgeon at Roosevelt Hospital and the College, with Dr. Joseph A. Blake, and founded, with him, the research laboratory of Surgical Pathology at the College. In 1913, he resigned from Roosevelt Hospital and became Surgical Director of the Presbyterian Hospital.

He was one of the original members of the Society of Clinical Surgery and its first president. He was also a member of the American Association of Genito-Urinary Surgeons, the New York Academy of Medicine, the New York Surgical Society, the Société Internationale de la Chirurgie, and the Société Internationale d'Urologie. In 1913, he was President of the Clinical Congress of Surgeons of North America, which later became the Clinical Congress of the American College of Surgeons. He was a member of the American Medical Association, and the American Urological Association. He was consulting surgeon at the City, Roosevelt, Presbyterian, St Mark's, St Vincent's, Woman's and Knickerbocker Hospitals, and the Manhattan Eye and Ear Infirmary of New York City, the House of the Holy Comforter, Flushing, Muhlenberg Hospital, Plainfield, the Perth Amboy Hospital, and Christ's Hospital, Jersey City.

Doctor Brewer, in addition to many articles on anatomic and surgical conditions, especially diseases of the kidney, gallbladder and large intestine, was the author of "Textbook on Surgery" (3 editions), and "Surgical Diagnosis."

On May 15, 1917, he sailed for overseas as director of Base Hospital Unit No. 2, which took charge of No. 1 General Hospital, B. E. F., at Étretat, France. He served with an operating team at Casualty Clearing Station No. 4 in the Passchendaele campaign in the summer of 1917. In February, 1918, he was made Consulting Surgeon to the 42nd Division, A. E. F., and later, chief consultant in Surgery to the First Corps and still later to the First Army, serving in the area of the advance in the Chateau Thierry, St. Mihiel and Argonne campaigns. He was later made Officier de l'Ordre de la Couronne (Belgium).

In 1916, Hamilton College conferred upon him the degree of LL.D., and, in 1929, he received from Columbia University the degree of Sc.D. (hon.). In 1920, he was made an honorary fellow of the Royal College of Surgeons of Ireland.

In 1928, Doctor Brewer retired from the practice of surgery, and immediately went to France to renew his interest and study of anthropology. Soon after his return he was made Research Associate of Somatic Anthropology at the American Museum of Natural History.

Early in 1937, it became evident that he had a neoplasm of the bladder. Although this was held in check by radiation for almost two years, in December, 1939, it became rapidly worse and he died quietly on Christmas Eve, 1939.

WILLIAM DARRACH

ALEXIUS McGLANNAN, A M , M D , LL D

1872-1940

DR ALEXIUS McGLANNAN died at his home, 115 West Franklin Street, Baltimore, Sunday, February 25, 1940, after an illness of considerable duration Doctor McGlannan was born in Baltimore, July 24, 1872, his parents



ALEXIUS McGLANNAN, M D

being Alexius W McGlannan and Agnes Veronica Gallagher McGlannan His preliminary education was received at Calvert Hall College, and he was graduated in medicine by the College of Physicians and Surgeons, now combined with the University of Maryland, in 1895, and soon became actively engaged in teaching in this institution

At first he seemed inclined to medical subjects, with a particular interest in chemistry, but soon decided that surgery was to be his life's work and became connected with this department, quickly working his way upward. He had the conception, more universally stressed by many later, that the study of pathology is an important foundation to good surgery, and became rather closely associated with the late Dr Joseph C Bloodgood in his laboratory at the Johns Hopkins Hospital, and in his clinical work at St Agnes Hospital. His emphasis on pathology in his operative clinics, ward classes and lectures was a distinguishing characteristic of his teaching.

Doctor McGlannan's great energy, his fidelity to his work, and an unusual memory, soon bore fruit in rapid advancement in his chosen specialty. By 1915, he had become Professor of Clinical Surgery and Surgical Pathology at the College of Physicians and Surgeons. In 1930, he was made Professor of Surgery at the School of Medicine, University of Maryland, the two schools having been combined. In 1926, he was made Chief Surgeon of Mercy Hospital, Baltimore, where most of his work had been done and where he advanced step by step.

These positions entailed so much work that he eventually declined to operate except in the hospital with which he was so closely allied and for which he did so much, though he was on the Staffs of several others. In 1933, his health became impaired and necessitated curtailment of his activities, but by this time, he had accomplished a prodigious amount of work and achieved many honors. In addition to the positions already mentioned, he had been honored by numerous offices in the Medical and Chirurgical Faculty of Maryland, doing almost unlimited work on its committees, and was elected its President in 1929.

In addition to the City and State Societies and the American Medical Association, he was a member of the American Surgical Association, Southern Surgical Association, American College of Surgeons and American Gastro-Enterologic Association, and contributed many papers to these societies and to medical journals. In fact, it might be said that during his active years, besides the operative work of a large clinic, much teaching and caring for a large private practice, he wrote a great deal. One sees his articles in *Systems of Surgery and Medicine*, and his name in many bibliographies. The number of his published articles totals nearly 100.

Apparently, Doctor McGlannan felt that "opportunity is kind but only to the industrious." He had none of the usual avocations, such as golf, hunting or fishing, though he did some boating on Saranac Lake where he spent the summers at his elaborate camp. He did not drink, smoke or play cards. General reading and music were his recreations. He never ceased studying, even when he no longer operated.

Doctor McGlannan's reading was of a wide range with Surgery as the central theme, but he seemed to gather information easily and retain it permanently about all manner of subjects. This naturally added to his value

as a consultant in diagnosis and treatment, and enabled him to, surpassingly well, avoid being the type of surgeon who is only an operator

Doctor McGlannan's first wife, who was Miss Anna Maria Crean, died in 1902. They had one son, Alexius McGlannan III. In 1907, he married Dr. Sallie Porter Law, who was graduated in medicine at the Johns Hopkins Medical School that year but never practiced. Mrs. McGlannan is a gifted artist and illustrated Doctor McGlannan's surgical papers. There were no children by this marriage. He is survived by Mrs. McGlannan, his son by his first marriage, and nieces and nephews.

One could pay tribute to Doctor McGlannan's ability, his industry, his accomplishments in surgery, or his devotion to the Roman Catholic religion and his exemplary life, but to many colleagues, house officers, students, and countless patients, his outstanding characteristics were friendliness and kindness and, above all, charity. He lent strength to the quotation, "Charity suffereth long and is kind, charity envieth not, charity vaunteth not itself, is not puffed up."

WALTER D WISE

GOVERNMENT TO NEED TEMPORARY AND PART-TIME CIVILIAN MEDICAL OFFICERS

THE expansion of the army creates a need for about 600 civilian medical officers in various grades for temporary and part-time service. The duties of full-time officers will be to act as doctors of medicine in active practice in hospitals, in dispensaries, and in the field. The duty of part-time officers will be to report for sick call at a fixed hour each day and to be subject to emergency call at all times.

The Civil Service Commission in making this announcement calls particular attention to the fact that part-time officers will be able to continue their regular practice. In order that this may be done, appointments to the part-time positions will be made of medical officers in the vicinity of the place of duty.

Information concerning these positions may be obtained from the Secretary of the Board of U. S. Civil Service Examiners at any first- or second-class post office, or from the United States Civil Service Commission, Washington, D. C. Physicians are urged to apply at once. This work is of the greatest importance to the success of the National Defense program.

AUGUST 31, 1940

EDITORIAL ADDRESS

Original typed manuscripts and illustrations submitted to this Journal should be forwarded prepaid, at the author's risk, to the Chairman of the Editorial Board of the ANNALS OF SURGERY

Walter Estell Lee, M.D.
1833 Pine Street, Philadelphia, Pa.

Contributions in a foreign language when accepted will be translated and published in English.

Exchanges and books for review should be sent to James T. Pilcher, M.D., Managing Editor, 121 Gates Avenue, Brooklyn, N. Y.

Subscriptions, advertising and all business communications should be addressed

ANNALS OF SURGERY
227 South Sixth Street Philadelphia, Pa.

SYMPOSIUM
ON
ANEURYSMS AND VASCULAR
SURGERY

PRESENTED BEFORE
THE AMERICAN SURGICAL ASSOCIATION

St Louis, Mo , May 2, 1940

PERSONAL EXPERIENCES IN VASCULAR SURGERY

RUDOLPH MATAS, M D , New Orleans, La

SURGICAL TREATMENT OF ANEURYSM OF THE ABDOMINAL
AORTA

I A BIGGER, M D , Richmond, Va

ANEURYSM OF THE ABDOMINAL AORTA SUCCESSFULLY
TREATED BY LIGATION

DANIEL C ELKIN, M D , Atlanta, Ga

FINAL REPORT OF THE FIRST SUCCESSFUL LIGATION OF
THE ABDOMINAL AORTA FOR ANEURYSM (Illustrated)

RUDOLPH MATAS, M D , New Orleans, La

CLINICAL AND EXPERIMENTAL OBSERVATIONS ON
ARTERIOVENOUS FISTULAE

EMILE HOLMAN, M D , San Francisco, Calif

EXPERIMENTAL STUDIES OF GRADUAL OCCLUSION OF
LARGE ARTERIES

HERMAN E PEARSE, M D , Rochester, N Y

PREVENTION OF ISCHEMIC GANGRENE IN OPERATIONS
UPON ARTERIES BY CHEMICAL SECTION OF SYMPATHETICS

I MIMS GAGE, M D , and ALTON OCHSNER, M D , New Orleans, La

CIRCULATORY DISTURBANCES PRODUCED BY ANGIOMATA
OF LEGS, ASSOCIATED WITH VARICOSE VEINS

WALTER E LEE, M D , and NORMAN E FREEMAN, M D , Philadelphia, Pa

DISCUSSIONS BY

RUDOLPH MATAS, M D
EMILE HOLMAN, M D
FREDERICK L REICHERT, M D

I A BIGGER, M D
JOHN HOMANS, M D
MONT R REID, M D



PERSONAL EXPERIENCES IN VASCULAR SURGERY *

A STATISTICAL SYNOPSIS

RUDOLPH MATAS, M D

NEW ORLEANS, LA

HISTORICAL PREFACE—Since I am circumscribed by the title of this paper to a summary of my personal experience in the surgery of the blood vessels, with special reference to aneurysm, I trust it will not be regarded as inappropriate that I should begin with a statement of the historical and statistical data upon which this experience is based

Though the surgery of the blood vessels, meaning by this the operations upon the great arteries and veins that require anatomic knowledge and surgical skill for their performance, constituted one of the most notable and distinctive chapters in the history of surgery in Louisiana, it is not until a relatively late period in the state's history—as late as 1825—22 years after the territory now known as Louisiana had become a possession of the United States, that the first records of such operations appear in the annual reports of the Charity Hospital of New Orleans. Prior to this date, the most careful inquiry into the history of the colonial period, through the 104 years of the alternate French and Spanish dominations (1699–1803), fails to disclose any documents or data that would throw light on the status of surgery in the colony, except for the laws that regulated its practice and which, as late as 1770 (during Governor O'Reilly's administration), discriminated between the physician and the surgeon, and made the latter subservient to the former. This distinction was never strictly observed in the colony, except in the case of the so-called "barber-surgeons," and had ceased altogether after the Louisiana purchase by the United States, in 1803. Though it would seem strange and singular that the records of the early military and other well-qualified colonial surgeons, of great experience in the constant warfare of the colonists with their savage foes and their European rivals, should have been so barren of historical commentaries or official reports, it is none the less true that no records of their surgical services and activities are in existence.

In contrast to the lack of information on the surgery of the colonial period, the medical historian finds a great wealth of material in the epidemic and endemic fevers and other pestilential diseases that frequently ravaged the

* Presented by title before the American Surgical Association, St. Louis, May 1, 2, 3, 1940

population and which, combined with other great calamities (war, famine, floods, hurricanes, fires), often threatened the struggling colony at New Orleans with extinction. These major evils so completely overshadowed the casualties and incidents of surgical practice that no references to the latter are found in the official reports of the colonial governors, or in the later publications of the historians of that period. In the absence of all records, we can well imagine that, whatever the modes of surgical practice adopted by the French colonial surgeons, they were largely, if not exclusively, modeled after the pattern of the schools of France, the mother country. During the Spanish interregnum (1766-1803) medical practice remained essentially French and unchanged, except in the purely official relations. It is, however, a notable fact, worthy of record, that the first book printed in Louisiana (1796) and translated into French for popular distribution, was a medical treatise, written in Spanish, by Dr. Joseph Masdevall,* physician to King Charles III, and to the royal household.

Surgical practice in Louisiana was, therefore, a mere reflex of the surgery in France as it developed during the eighteenth century, and it is only to this source that we can look for information on the status of surgery in Louisiana and in the other French colonies of the period. When we consider that the tourniquet, invented by Morel (1674), and its modifications by Pettit and others, had not come into general use until the first decade of the century, and then used only to control hemorrhage in amputations, that the ligation of arteries was almost exclusively confined to hemostasis in amputations, that hemostasis in bleeding wounds was largely a matter of local vegetable, animal and mineral styptics, among which flourished the "hemostatic plug or 'button'

* "Medicaments et Précis de la Méthode de M. Masdevall, Docteur medecin du Roi d'Espagne Charles IV, Pour guerir Toutes les Maladies, Epidemiques, Putrides, et Malignes, Fievre de Différents Genres, etc, pour en Preserver. Divises en Paragraphes et en Numeros Correspondants, à l'Usage des Familles Depourvues de Medecins. Prix 4 Escalins Broche, chez Louis Duclet, Imprimeur, a la Nouvelle Orleans, 1796. Avec Permission du Gouvernement." The book is dedicated to the "very illustrious" Baron de Carondelet, Governor of Louisiana.

Masdevall stood high in Spain as a sanitarian and epidemiologist, with special experience in the malignant "pestilential and putrid fevers" (typhus, malaria and yellow fever), in the treatment of which he claimed and was credited with great success. The book printed in New Orleans was intended as a popular guide for the direction of the colonists in the Spanish possessions in the treatment of the malignant fevers. It was published and distributed by order of the King. The chief ingredients of his polypharmaceutical formula (Masdevall's potion or electuary) were powdered cinchona bark and tartar emetic in small doses. His great merit, and probable secret of his success, was his vigorous condemnation of bloodletting in all its forms, at that time the universal practice. He was President of the Spanish Academy of Medicine, Madrid (1799). He never visited Louisiana. Masdevall was born in Figueras, Catalonia, Spain, and graduated from Cervera and Montpellier. The precise date of his birth is unknown, but it was sometime during the decade 1740-1750. He died at Trujillo (Northern Spain) in 1801, while accompanying King Charles IV and the royal family to the frontier in the prelude to the Napoleonic invasion. (For biography and other data see Garcia del Real, *Historia de la Medicina en Espana*, 1 vol., 404-418, Madrid, 1921, also Jaime Pi-Sunyer, in *La Medicina Catalana*, 8, Nos. 47-48, p. 1-2, August-September, 1937.)

of vitriol, or alum" applied as a surface plug to bleeding vessels—and the actual cautery as a supreme resource, that the ligation of the great arteries, in continuity, for the control of hemorrhage and for the cure of aneurysm was not practiced until 1786, when John Hunter, in England, Desault, Anel, Biasdor, Deschamps, in France, contemporaneously advocated and practiced it, that the first knowledge of arteriovenous aneurysms came with William Hunter, in 1761—and that some of the ablest surgeons of Europe (Percival Pott, 1790, *et al*) preferred amputations to the ligation of arteries for the cure of aneurysm, that the rules for the ligation of wounded arteries which had been formulated by Larrey, in France, and Guthrie, John Hunter and John Bell, as the result of their observations in the Napoleonic campaigns, were not generally known or universally adopted until after 1825–1840—it is evident, in view of the lateness of these advances, that no ligations involving the blood vessels could have been performed (apart from amputations) during the colonial period, or, at best, only at the close of the eighteenth and beginning of the nineteenth centuries

Furthermore, the conditions that prevailed in New Orleans, the only center of medical activity in the vast territory or "province" of Louisiana, were not at all favorable or conducive to any unusual or daring surgical enterprises. In 1803, when Louisiana was transferred to the United States, the total population of the city was little over 8,000 and, of these, half were slaves or free blacks. There were in all not over 20 regular graduates or qualified medical practitioners. Apart from the Spanish Military Hospital, and the Leper Hospital, there was only one hospital in effective operation, and that was the Charity Hospital of St Charles (San Carlos), created in 1784 by a philanthropic Spaniard, Don Andres Almonester y Rojas, to replace the first "Hôpital des Pauvres," a small establishment of a dozen beds, which had been founded by the legacy of an humble French sailor, Jean Louis, in 1736, 18 years after the foundation of New Orleans, in 1718. This had been destroyed by a hurricane in 1779, and the Almonester Hospital itself (with 35 beds) was also consumed by the great fire which swept over the city in 1809. The Spanish Military Hospital, the old "King's Hospital" founded by Bienville and enlarged by the Spanish Governor O'Reilly, in 1770, for sick soldiers and government officials, became obsolete soon after the transfer to the United States, in 1803. Whatever records of the operations performed in these hospitals that could have given an insight into the surgical practice of that period were lost. Furthermore, the messages of the French and Spanish governors to their governments referred only to general medical conditions that affected the health of the colony, but never touched upon matters of technical interest to the profession. Again, we may say that any incentives to the publication of their experiences that the colonial practitioners might have had were denied them by the fact that no printing press was in operation in Louisiana until 1764. The first newspaper published in Louisiana was the *Monteur de la Louisiane*, which was started near the close of the century, in 1794. Again we may say that the chief stimulus to the exchange and discussion of medical experiences

was wanting for lack of medical organization during the colonial régime. The first attempts at a medical society by O'Reilly in his proclamation of 1770, and by LeDuc in 1804, proved abortive and were not renewed until 1817, when the "Société Médicale de la Nouvelle Orléans," which was composed of the French speaking physicians, was organized (first meeting, August 19, 1817), this was followed in less than three years by the "Physico-Medical Society" (incorporated February 16, 1820), representing the English speaking doctors.

The first medical journal published in Louisiana was the *Journal de la Société Médicale de la Nouvelle Orléans*, which made its first appearance in 1839, as the organ of the French Society of the same name. The next journal was the *New Orleans Medical Journal*, edited by Fenner and Hester in 1844, which merged the year after (1845) with the *New Orleans Medical and Surgical Journal*, which has remained, ever since, as the main repository of the medical history of the state.

We see by all this that, even after the memorable battle of New Orleans on January 8, 1815, there were no medical societies or publications in which events of medical and surgical importance could have been discussed or recorded. Not even the battle of New Orleans, with its nearly 2,000 British killed and wounded, has left behind it any history or historian whose observations could have profited the profession by the study of the medical and surgical lessons gathered from that epochal battle. But there was no Larrey or a Guthrie on either the British or American side to extract out of the carnage of battle something useful for the benefit of humanity and for the progress of surgery, as these great military surgeons had done out of their experience in the Napoleonic Wars.

LOUISIANA PURCHASE AND TRANSFER TO THE UNITED STATES

ITS EFFECT ON THE MEDICAL AFFAIRS OF THE TERRITORY

The radical changes in the political and governmental status of the vast territory which followed the acquisition of the French colonial "Province of Louisiana" by the United States, in 1803, and which became more definite and stabilized when Louisiana was admitted as a state of the Union, in 1812, had a profound effect on the affairs and future of the medical profession of the state as upon everything else.

With the removal of all barriers and restrictions to immigration and commerce with the Anglo-American colonies and foreign countries, which had been imposed by the colonial governments for over a century, the population of New Orleans and of the country districts (parishes) rapidly increased and a new era of business activity, economic and agrarian prosperity was inaugurated which benefited all classes. Paradoxical as it may seem, the Creole descendants of the old French colonists, whose fortunes had remained stagnant during the Colonial regime, now became the greatest beneficiaries of the administrative changes instituted by the new American government. With the free navigation of the Mississippi, the river traffic increased enormously, and with a free outlet to the sea, the unrestrained maritime commerce with foreign countries soon made New Orleans one of the busiest and most pros-

perous ports of the United States. Likewise, a steady stream of hardy Anglo-American pioneers from neighboring and border states, especially from Kentucky, Tennessee, Missouri, Arkansas and Mississippi, soon began to flow into the northwest parishes of the newly created state, and established new English-speaking settlements in parts which had been scarcely touched by the original French and Spanish colonists. The population of New Orleans, which was a little more than 8,000 in 1803, rose to 29,000 in 1821, and, in 1830, had grown to 49,826, of which 29,580 were whites and 21,280 were Negroes or free slaves. The present state of Louisiana (originally defined as the territory of Orleans) comprised a total population of 215,739, of whom 89,441 were whites, 16,710 free colored, and 109,588 slaves. Ten years later, in 1840, the population of New Orleans had increased to 102,204, and that of the state as a whole to 352,411, of whom 158,457 were white inhabitants. The white population was then made up of Anglo-Americans, French and Spanish colonists and their Creole (white) descendants, together with a large proportion of Germans, and a good sprinkling of almost every other nation of the globe.

With this rapid increase in population came many enterprising medical practitioners who hailed from the recently established American schools in the northeastern and southern states, who found lucrative practices in the new Anglo-American population. Owing to the practical cessation of French and Spanish immigration, they soon obtained the ascendancy, not only in medical practice, but in the administration of the medical institutions of the state, which, during the colonial period, had been almost exclusively in the hands of graduates of Paris and other French medical schools.

As the population increased, the need of greater facilities for the care of the indigent sick and injured of New Orleans and of the commonwealth became more pressing. As previously stated, the only charity hospital in active operation at the time of the Louisiana purchase, in 1803, was the Almonester Hospital (San Carlos). This hospital continued in the service of the poor until 1809, when it was consumed in the great fire that swept over the city at that time. After a long interval of great hardship to the poor of the community, a third Charity Hospital, this time erected by the state and not by private beneficence, was built on Canal Street in 1815-1816. It had 125 bed-capacity, and continued to be the main agency for the city's charity to the sick poor until 1832, when it was replaced by a new and spacious building of 540 bed-capacity, which the state erected at the site of the present unit on Common Street, now Tulane Avenue.

At the time of its erection, this hospital was the largest and oldest hospital in the South and probably in the United States. Six years after it had been built, 1848-1849, it was overcrowded, and it became necessary to enlarge the original plant by the addition of new buildings to provide adequate accommodation for the constantly increasing number of indigent sick and injured of the rapidly growing population of the city and state. In 1848, it could accommodate 1,000 patients, and had a yearly average of 11,000 to 13,000 admis-

sions It was then the largest hospital in existence It stood fair comparison with those of Europe and America At that time, in Paris, the Hôtel Dieu had a capacity of 810 beds and La Charité 494 beds, and these were the largest medical charities in that world metropolis

After serving for more than 103 years, the main building and several other old buildings were demolished in 1936 to make place for the present New Charity Hospital, opened July 1, 1940 It is in the course of the evolution and growth during these 103 years that this institution has attained the magnificent proportions that have made it the largest, as well as the oldest and best known public charity in the Southwest Its history coincides with the evolution and progress of surgery, and its practice reflects the progressive and revolutionary changes that have characterized the transition from the old to the new surgery, in this centennial period *

* * * * *

It may be safely said that, from its beginning in 1832 to the late seventies, the Charity Hospital stood as an isolated but towering refuge for the indigent sick and injured, not only of Louisiana but of the sparsely settled country bordering on the banks of the lower Mississippi, who could be transported by the river routes and scant railroad facilities of that time, all the way from Cairo, Illinois to New Orleans The relatively unsettled and lawless state of the country all along the Mississippi Valley following the accession of Louisiana and the opening of the newly acquired territory in the South and great Southwest, usually provided an abundant clinic of wounds of all sorts, many of these involving the large peripheral blood vessels, including their sequelae, the arterial and arteriovenous aneurysms It was these that furnished the most interesting material for the display of anatomic knowledge and surgical skill of the surgeons who flourished at the Charity Hospital and who, in the thirties and forties, were beginning to establish a widespread reputation for New Orleans as the center of the greatest medical and surgical activity in the South and Southwest

The history of the Charity Hospital, as evolved since 1832, in its present and prodigiously developed plant, is practically contemporaneous with the foundation of the first Medical College of Louisiana, which was organized, in 1834, and continued later (1847-1884) as the Medical Department of the University of Louisiana, and, since 1884, as the Medical School of the Tulane University of Louisiana As a result of the combined activities of its first faculty, who constituted the medical staff of the hospital, and the great and growing resources of the hospital as a school of incomparable facilities for

* According to the last report, which appeared in March, 1940, the New Charity Hospital is equipped with 3,300 beds, 40 operating rooms, a personnel of 400 visiting physicians and surgeons, 171 interns, 105 resident physicians, 400 graduate nurses, 315 student nurses, also technicians and numerous nonmedical workers included in a paid staff of about 2,200 Statistics for the last year, ending July 1, 1939, show a total of 58,899 admissions, 26,575 new cases and 404,996 total visits in the Out-Clinic, 44,957 cases in the accident room, and 23,473 operations performed in the operating rooms

clinical instruction, the hospital became, not only the fountain source of medical education in the South, but also, in view of the surgical achievements of the renowned surgical teachers who flourished in it, the very cradle and nursery of surgery in Louisiana. In fact, the history of surgery in so far as Louisiana is concerned, really dates back to the foundation of the Charity Hospital in 1832, for whatever achievements in this field of medicine may have been accomplished by previous generations have been lost and remained unrecorded until the first records of this hospital brought them to light and made them available to the medical historian. It is, therefore, in collecting the data of the history of vascular surgery in which we are now especially concerned, that we are compelled to begin with the first records of the Charity Hospital as the chief and only foundation for our research.

We must bear in mind that it was not until 1845 that anesthesia by ether was discovered, and chloroform in 1847, and that it was not until late in the seventies that the antiseptic doctrine which Lister had enunciated in 1867 was recognized and, even then, quite indifferently and skeptically applied in current practice. Consequently, the practice of surgery was largely circumscribed to the extremities in which fractures, dislocations, amputations, the ligation of arteries and the treatment of ulcers and wounds constituted the chief work of the surgeon. The limitations of surgery were indeed then very great and, as late as 1881, did not constitute more than 3.2 per cent of the total medical treatment given by the hospital. There was then no abdominal or gynecologic surgery, no thoracic surgery, no orthopedic or neurologic surgery, nothing except fractures, dislocations and amputations, lithotomy or cutting for stone, an occasional trephining, rarely a celiotomy for ovarian tumor, strangulated hernia, or an operation for cataract, to divert the attention of the surgeon away from the extremities or to extend the excursions of surgery beyond them. And this was the status of surgery throughout the world until the last quarter of the nineteenth century, when the genius of Pasteur and Lister emancipated surgery and suddenly expanded its dominion and its therapeutic resources to its present limitless horizon. It is not surprising that the surgeons of the later eighteenth and of the nineteenth centuries should have cultivated a special interest in the surgery of the blood vessels which provided the most inviting field for the display of anatomic knowledge and for the accomplishment of daring feats in surgery which, at that time, were justly regarded as the highest attainments of the art. The surgeons who attained the greatest fame throughout the world had won their reputations largely through their achievement in the surgery of the blood vessels. The great names of Desault, Dupuytren, Anel, Deschamps, Brasdor, Lisfranc, Velpeau and Broca, in France, Valsalva, Lancisi, Scarpa and Porta, in Italy, John and William Hunter, Charles and John Bell, Abernethy, Guthrie, Sir Astley Cooper, Liston, Hodgson Syme, Wardrop, Billingham and Compton, in the British Isles, Graeffe, Purmann, Dieffenbach, Stromeyer, Langenbeck and Hutter, in Germany, Pirogoff in Russia. In America, the

daring and success of the early New England and Eastern surgeons in the ligation of the carotids, subclavians, iliacs, femorals, etc., were far in advance of the European surgeons, conspicuous among these were Wight Post, W F Cogswell, Amos Twitchell, J S Dorsey, James McGill, W Gibson, Willard Parker, and above all, Valentine Mott⁺—*facile princeps* of the vascular surgeons of his time—are inseparably bound with the most notable achievements of the preanesthetic and prelisterian period. It is natural, therefore, that the surgeons and teachers at the Charity Hospital living in the same period should have yielded to identical aspirations and tendencies that dominated the surgical world and that incited them to devise and perform operations for the cure of aneurysms which were new and daring for that age. Thus, we see the first successful ligation of the common iliac artery for aneurysm performed at the Charity Hospital, in the early thirties, by Charles Luzenbeig (1808–1848), the first professor of surgery in Louisiana, and again by his successor, Warren Stone (1808–1872), who was the first to use a metallic ligature (silver wire) to occlude the same vessel, in order to avoid the dangers of the classic, but septic, silk ligatures. Later, Wederstrandt repeated the same feat, and Wedderburn ligated the third subclavian, while Stone successfully attacked the aneurysms of the extremities, including traumatic aneurysms of the gluteal and vertebral arteries, in the forties and fifties. Other ligations were performed in the same period by Picton, Armand Mercier, Daiet, Compton, Choppin, Schuppert, and still others, too numerous to mention. But the crowning event in the prelisterian period of the hospital's history was the first successful ligation of the innominate for a subclavian aneurysm by Andrew Smyth in 1864—which gave this illustrious surgeon, and the hospital, an enduring and widespread international fame.

The descriptions of these operations, as they were performed by these enterprising pioneer surgeons, in the difficult and unprepared conditions of surgical technic which prevailed in the preantiseptic period, read to the surgeon of to-day as a sort of adventurous epic well tinctured with heroic flavor.

* * * * *

* In his memoir of Mott (1785–1865), published in 1868, Professor S D Gross writes: "No Surgeon, living or dead, ever tied so many vessels or so successfully, for the cure of aneurysm, the relief of injury or the arrest of morbid growths. The catalogue, inclusive of the celebrated first ligation of the innominate artery (1818) (succumbed to secondary hemorrhage on the 28th day), comprises eight examples of the subclavian artery, 51 of the primitive carotid, two of the external carotid, one of the common iliac (first successful) 1827, six of the external iliac, two of the internal iliac, 57 of the femoral and ten of the popliteal, in all, 138." Besides the ligations, he had 165 lithotomies and over 1,000 amputations to his credit.

Sir Astley Cooper, one of his early teachers, spoke of him as "the surgeon who had performed more of the great operations of surgery than any man living, or that ever did live" (Gross' *Memoirs*, 1 c., and in *Century of Am Surgery*, Lea, Phila., 1876, F Garrison, *Bulletin N Y Academy of Med*, August, 1925, 2nd series 1.)

It was my good fortune to begin my internship in the Charity, at the very dawn of the Listerian era (1877), but I can well remember a number of amputation stumps with long, dangling ligatures attached like suppurating setons to the main arteries, as a sign that the short, buried, antiseptic ligature had not yet won the confidence of all surgeons.

Even in the seventies and early eighties, the fear of infection, suppuration and secondary hemorrhage which was an almost invariable sequela of the ligature for the cure of aneurysm, awed the surgeons and restrained them from any open attack on the aneurysms of the great vessels and led them to resort, when at all possible, to mechanical and bloodless methods such as indirect digital compression (Jonathan Knight, in the United States, and Belmas, in France, 1844), instrumental compression by various devices (W. Reid, 1875), flexion (Hart, 1857), needling, malaxation and wiring for the inoperable central aneurysms.

I had assisted as an undergraduate intern in the application of all these methods by my distinguished chiefs—T. G. Richardson, Samuel Logan, A. B. Miles, and particularly Dr. Edmond Souchon, whose valuable contributions to the surgery of aneurysms have left an enduring mark in the literature. It was only when the bloodless methods failed that the Hunterian ligature was adopted, usually, as a last resort. Incision of the sac after bipolar ligation and packing (Antyllus), or excision of the sac were not thought of except when rupture was threatened by infection and suppuration or sloughing, and even then an amputation was deemed safer by most of the staff. In the aortic and other central aneurysms, absolute rest in bed with a restricted diet and the administration of mercury, potassium iodide, opium or morphia for pain, and such circulatory depressants as veratrum viride, or aconite, following the ancient teachings of Valsalva, Jelliffe, Tuffnel and Billingham of the Irish school, was the only treatment—a mode of treatment which has not materially improved up to the present except for the benefits of the arsenical preparations, salvarsan, arsphenamine and bismuth, which undoubtedly exercise a prophylactic beneficial influence in arresting the aortitis or arteritis of syphilitic subjects when timely administered before the actual aneurysmal stage is reached.

In this connection, the rise and spread of the *pathogenic aneurysms* as a manifestation of arterial disease, particularly involving the aorta and its large central branches—when coupled with their greatly increased prevalence in the Negro race since emancipation—is one of the most striking features of the Charity Hospital experience.

It is a well-established fact that the aneurysms of the aorta were a relatively negligible factor in the mortality of the Southern states before the Civil War, with even less incidence in the Negro slave population.*

* For a full description and appreciation of the great value and importance of the Charity Hospital as a center for the study of the comparative pathology of the white and Negro races, see the author's monograph on "The Surgical Peculiarities of the American Negro. A statistical inquiry based upon the records of the Charity Hospital." Trans. Am. Surg. Assn., 14, 130, 1896.

At the Charity Hospital, during the period 1825-1831, only two aneurysms were recorded in 15,707 total admissions, or one aneurysm to 7,853 admissions. In the decade 1865-1875, 65,935 total admissions yielded 63 aneurysms, or 1 1,046 admissions. In the decade 1884-1893, a total of 199 aneurysms were admitted, whites 143 (71.86 per cent), or 1 312.5, and colored 56 (28.14 per cent), or 1 344.8. In 1904-1931 (27 years) a total of 1027 aneurysms were admitted, or 1 335 surgical admissions, 1 1,166 total white admissions and 1 329.9 total colored admissions.

In the five years, 1935-1939, a total of 412 aneurysms were admitted, or 1 742 total admissions and 1 296 surgical admissions. In this group the ratio was one white to 3.5 Negroes. Of these 412 aneurysms, 90 per cent were pathogenic, chiefly aortic, and of these, 73.3 per cent were Wassermann positive. Of the total 412, only 45, or 10.9 per cent, were regarded as surgical and were operated upon.

It is worthy of note that, while the surgical or operative cases have not kept pace with the enormous increase in the "medical aneurysms" (the pathogenic, inoperable, chiefly aortic, aneurysms), the statistics of the operated cases show the extraordinary improvement that has been wrought in the results of the operations by modern methods. During the 52 years, 1826-1877, (including the preanesthetic and preantiseptic periods), 175 aneurysms were admitted for treatment at the Charity Hospital. During this period the methods of ligation and bloodless methods of indirect compression were in vogue. There were in all 68 deaths, or a gross mortality of 45.3 per cent. Collective staff statistics of Charity Hospital from the files in the record library show that, from August, 1905 to July, 1934 (29 years), 234 patients were operated upon for aneurysms by 37 surgeons (including 101 by Dr. Matas). Different methods were employed, including ligation, extirpation and endo-aneurysmorrhaphy. There were 38 deaths, or a gross mortality of 16.2 per cent.

The result of this inquiry shows (1) That aneurysm as a disease and not trauma, has increased 13 times over its incidence 100 years ago, (2) that this increased prevalence is particularly apparent in the colored population (3½ times more prevalent in the Negro), (3) that this increased prevalence is due to the vast preponderance of the pathogenic aneurysms of arterial disease (90 per cent), while the traumatic aneurysms have gained very little in prevalence in the last 40 years (ten pathogenic to one traumatic), (4) that fully 75 per cent of the pathogenic aneurysms were aortic or central, (5) that 73.3 of these occur in Wassermann positive subjects, and (6) apart from the increased incidence of aortic aneurysms due to roentgenographic studies and greater facilities for diagnosis, there has been an actual increase in the prevalence of the disease, confirmed by postmortem evidence*. That, while the incidence of aneurysms has vastly increased in the last 60 years, it has been chiefly in the aortic, internal or medical aneurysms, with very little increase in the operable or surgical peripheral aneurysms, since we have had no condition of warfare which would increase traumatic aneurysms.

As far as the arteriovenous aneurysms are concerned, the old teaching regarded them as relatively benign and not liable to rupture—a tradition which lingered from the days of William Hunter (1774), they were allowed to remain undisturbed except by purely mechanical methods of compression. When complicated by large varicose sacs, by infection or by other disabling varicosities they were attacked by the open method, only as a last resort. When surgery was required, the proximal artery was ligated, but, as experience too frequently proved, with no cure and often gangrene of the limb. It

* Ref. I. I. Lemman. *Am Jour Med Sc*, vol 105, No 5, 1916

was only after the great treatises of Paul Broca, in the fifties, and Pierre Delbet and von Bramman, in the eighties, that the principles underlying the cure of arteriovenous aneurysms were clearly understood and that the extirpation of the fistulous segments or the quadruple ligature were more frequently resorted to

None the less, the complete ignorance of the profession regarding the secondary and evil effects of arteriovenous fistula upon the heart and circulation which came as a revelation with the vast experience of the World War, continued until comparatively recent times, to protect these aneurysms from active and aggressive surgical action. We now know that every arteriovenous fistula of large size and which involves the greater blood vessels is, apart from its disabling local and regional effects, a perpetual menace to the integrity of the circulation, and that sooner or later, according to the size of the fistula and other correlated factors, the heart will suffer serious organic changes—dilatation, myocardial degeneration with a terminal fatal decompensation

* * * * *

Going back to my personal experience, I would state that my internship in a hospital where the surgery of the blood vessels had become a proud historic tradition, my association with the great surgeons and teachers just mentioned, who were especially concerned with the cure of aneurysm, and the anatomic experience that I had acquired early in my career as demonstrator of anatomy for over ten years in the dissecting rooms of the medical school, all combined to give me a special interest in vascular pathology and thereby to utilize the unusual opportunity given me to study, clinically and surgically, the ever fascinating problems that for practically 60 years have presented themselves to me as a visiting surgeon of the Charity Hospital and of the other local institutions with which I have been associated

In the course of these years the opportunities for the treatment of aneurysm and other vascular lesions and diseases rapidly increased and, as my special interest and experience in the treatment of these cases became known to my associates, pupils and friends, I was favored by their kindness in referring many in and out of town patients, some from distant states, who increased my statistics out of proportion to the number that would have been furnished to any single operator by the local surgical population. In earlier years I operated upon a number of patients in private houses, but, as our hospital facilities increased I operated almost exclusively in the various hospitals with which I was connected. (In addition to the Charity Hospital, my list includes operations performed at the Hotel Dieu, New Orleans Sanitarium, which became the Presbyterian Hospital, the Eye, Ear, Nose and Throat Hospital, and Touro Infirmary.) After 1904 my practice was confined to the Charity Hospital and the Touro Infirmary

THE FIRST ENDO-ANEURYSMORRAPHY*

Prior to 1888, I treated the aneurysms and other allied vascular lesions that came under my care by the classical methods in vogue at the time, and in these the ligation on the hunterian or Anel principles predominated. But, on April 6, 1888, I operated upon a young male Negro for a very large traumatic (multiple gunshot) aneurysm of the brachial artery, extending from the armpit to the elbow, which opened my eyes to the possibilities of an entirely new method of conservative treatment which was to revolutionize my previous notions of aneurysmal surgery. In this case, the successive ligation of the main artery on the proximal and distal poles of the aneurysm had been followed by relapse, and it seemed to me, then, that I had no other alternative but to extirpate the sac. When I exposed the sac and emptied its contents, the failure of the ligations to control the circulation was easily explained by the appearance at the bottom of the sac of three large orifices corresponding to the collateral branches which opened into the sac in the segment of the artery included between the ligatures. It was evident that it was these collateral orifices that fed the sac despite the ligatures that had been placed at each one of its poles. I, at first, intended to secure these collaterals by excising the sac, but the branches of the brachial plexus of nerves were so densely incorporated in its walls that I could not have dissected them out and detached them, without serious damage, thereby paralyzing the arm. It occurred to me then that the easiest way out of this awkward dilemma was *to seal the orifices of all the bleeding collaterals by suturing them as we would an intestinal wound*, leaving the sac attached and undisturbed in the wound. This procedure was at once put into effect and the hemostasis was so perfect and satisfactory that it seemed to me strange that no one should have thought of so simple an expedient before.

This, then, was my first case of aneurysm treated by the method of intrasaccular suture which, with further experience and thought, I developed and systematized into the method of endo-aneurysmorrhaphy or intrasaccular suture, and which, in its three phases—the obliterative, the restorative and the reconstructive—is now associated with my name. My initial case was reported in the Philadelphia Medical News, October 27, 1888—now more than 51 years ago. But the first systematic description of the method was not reported until 14 years after this publication, 1902, at the meeting of the

* The spelling of the word "endo-aneurysmorrhaphy" is in accordance with the classical orthography of the dictionaries. This neologism was originally coined out of the Greek by me, in 1902, as descriptive of the eponymic designation "Matas operation" by which it was usually referred to in the literature. Many have adopted "endo-aneurysmorrhaphy" and others simply "aneurysmorrhaphy." Personally, I have abandoned the original form for the contracted "endo-aneurysmoraphy" or "endo-aneurismoraphy" which is equally descriptive and faithful to its origin, but much simplified by the elimination of unnecessary consonants, following the suggestion of the Carnegie Spelling Board. When the term is frequently repeated, the word is still further abbreviated by writing "endo-a," as in *endo-a, obliterative*, *endo-a, restorative*, *endo-a, reconstructive*.

American Surgical Association held in Albany that year, and published in the ANNALS OF SURGERY for February, 1903—now 37 years ago.* The appearance of this paper was followed by many published reports and personal communications from other surgeons at home and abroad who confirmed the practical simplicity and conservative value of the operation and gave it their commendation and support. Since the original report in 1902, I have published a number of statistical summaries which included my personal operations and the cases reported by other surgeons as these steadily increased and accumulated in the literature. Of these statistical papers, the most complete are: The report of 225 operations presented by invitation at the International Medical Congress held in London in 1913, the second is my Mutter lecture in Philadelphia, 1915 (289 cases), the third is my report to the French Surgical Congress held in Paris in 1922, when I reported 350 aneurysmorrhaphies, including my own personal cases. Again, in October, 1925, at the Clinical Congress of the American College of Surgeons, in Philadelphia, I was able to increase the collective experience in aneurysmorrhaphy to 478 recorded operations contributed by the surgeons all over the world. Of these, 65 had been performed in my own practice, including the arterial and arteriovenous aneurysms. Altogether, the surgeons of Louisiana, including my own cases had recorded over 110 aneurysmorrhaphies in all three of its modes, and of which approximately 80 per cent are of the obliterative type.

The collective results of these operations as they appear in the detailed summaries of my London (1913), Mutter lecture, Philadelphia (1915), Paris (1922), and Philadelphia (1925) statistics are, on the whole, very gratifying, and statistically superior to those of other methods resorted to for the same class of cases.

Since 1927, when the list of these operations, collected from the literature, had increased to 505, I have made no systematic search or compilation of cases reported in the literature. In fact, the operation has entered so largely into the current surgery of most countries that it has ceased to be a novelty and is reported only in exceptional cases.

Taken altogether, in all its modalities or phases, the restorative, the reconstructive, and the obliterative—the mortality (exclusive of the aortic aneurysms) did not exceed 4.5 per cent, the gangrene following operations for aneurysms of the extremities, 3.5 per cent, secondary hemorrhage, 1.6 per cent, and the relapses, chiefly in reconstructive cases, 1 per cent of the 350 operations reported to the French Congress in 1922. A far better showing, as a whole, than the statistics of the ligature or of extirpation which were so exhaustively compiled by Delbet and Mocquot, and by Monod and Van-

* In the interval between these years, further clinical and anatomic opportunities presented themselves for the study of aneurysmal sac-interiors, which led to an entirely new study of the morphology and variations in the anatomy of aneurysmal sacs, as fully described under "Morphology of the Sac" in my treatise on aneurysms, in Keen's Surgery. This study led to the subdivision of endo-aneurysmorrhaphy into its three varieties, as previously stated.

verts in France in 1911, and later by the German and Austrian surgeons during the World War as shown in my chapter on the "Military Surgery of the Vascular System," in Keen's Supplemental War-Volume VI, 1921 (See ref 44 this Bibliography)

In my statistics of 505 operations, which I had compiled from all sources up to 1927, I did not include the operations performed by the German and Austrian surgeons during the World War. Nearly 50 per cent of the cases of traumatic aneurysms reported by these surgeons as treated by the methods of intrasaccular suture, were *lateral* arteriorraphies performed in aneurysmal sacs or mature hematomas and in this way were virtually, in principle and technic, my restorative endo-aneurysmorrhaphies,* which I had described long before the war, but never credited, in Germany, until quite recently.

In the above statistics I have only referred to the operations performed by the method of aneurysmorrhaphy or intrasaccular suture, but I would like to make it clear that I do not treat all aneurysms by this or any one method. I do not apply endo-aneurysmorrhaphy to all aneurysms, on the contrary, I am decidedly eclectic, selective and discriminative in my practice, and this attitude is well shown by the following summary of my personal experience up to the present time.

CLASSIFIED SUMMARY OF 620 OPERATIONS UPON THE BLOOD VESSELS, PERFORMED FOR ALL CAUSES, BY RUDOLPH MATAS, M D, NEW ORLEANS, LA, BETWEEN THE YEARS 1888 AND 1940 †

PART I

ANATOMIC DISTRIBUTION

Operations upon the Common Carotid for Aneurysms or Aneurysmal Conditions (35 proximal, 18 distal), (proximal—24 arterial, 11 arteriovenous)	53
Operations upon the Common Carotid for Conditions other than Aneurysms	25
Operations upon the Internal Carotid (including the middle cerebral) (4 arterial, 3 arteriovenous)	7
Operations upon the External Carotid and its Branches for Aneurysms or Aneurysmal Conditions (5 arterial, 6 arteriovenous)	11

* Bier, A. On War Aneurysms. Handbuch Arztliche Erfahrungen in Welt Kriege Bd 1 Chirurg 2nd Part, 448-491, 1922, and C. Franz Lehrbuch d Kriegschirurgie 2nd Edit, 1939.

† This statistical summary is based on the author's classified tables of individual cases in which the essential facts are given in tabloid form for each patient, numbered in the order of his admission to the hospital or in the author's private records.

It is planned by the author to publish these tables conjointly with the descriptive text, in a series of papers devoted to the discussion of the material, and the conclusions drawn from his experience, in each of the regional or anatomic groups, as outlined in this summary.

Operations upon the External Carotid and its Branches for Conditions
other than Aneurysms

	321
Total Carotid Operations	417
Innominate	
6 provisional ligations (2 arterial, 4 arteriovenous)	
4 permanent ligations (all arterial)	
3 wiring with Colt's apparatus (all arterial)	13
Subclavian Aneurysms or Wounds (29 arterial, 7 arteriovenous)	36
Axillary (1 arterial, 3 arteriovenous, 4 injuries in the course of radical ex-	
tirpations of malignant growths)	8
Brachial (3 arterial, 2 arteriovenous)	5
Radial (3 arterial)	3
Hand (1 arterial, 1 arteriovenous)	2
Abdominal Aorta (1 ligation, 3 wired, 3 explorations with nothing done for	
aneurysm)	7
External Iliac and Iliofemoral (Iliofemoral—14 arterial, 4 arteriovenous,	
external and common iliac—3 arterial, 1 arteriovenous, 1 for injury in	
radical extirpation of femoral malignancy)	23
Internal Iliac (4 bilateral ligations as first stage of Wertheim operation)	8
Femoral (14 arterial, 18 arteriovenous)	32
Femoropopliteal (9 arterial, 3 arteriovenous)	12
Popliteal (42 arterial, including arterial accessory sac in an arteriovenous	
aneurysm, 4 arteriovenous, 1 circular angiography for myofibroma,	
2 amputations for popliteal injury, gangrenous on admission)	49
Tibial and Pedal (4 arterial, 1 arteriovenous, peroneal)	5
	<hr/>
Total	620

OPERATION FOR ANEURYSMS, ANEURYSMAL LESIONS (ANGIOMATA, CIRSOIDS
ETC), AND WOUNDS

Common Carotid	
35 proximal occlusions (24 arterial, 11 arteriovenous)	
18 distal occlusions (all arterial)	53
Internal Carotid (including middle cerebral)	
(4 arterial, 3 arteriovenous)	7
External Carotid and Branches (5 arterial, 6 arteriovenous)	11
Innominate	
6 provisional ligations (2 arterial, 4 arteriovenous)	
4 permanent ligations (all arterial)	
3 wiring (all arterial)	13
Subclavian (29 arterial, 7 arteriovenous)	36
Axillary (1 arterial, 3 arteriovenous)	4
Brachial (3 arterial, 2 arteriovenous)	5
Radial (all arterial)	3
Hand (1 arterial, 1 arteriovenous)	2
Abdominal Aorta (all arterial)	7
External, Common Iliac (3 arterial, 1 arteriovenous)	4
Iliofemoral (14 arterial, 4 arteriovenous)	18
Femoral (14 arterial, 18 arteriovenous)	32
Femoropopliteal (9 arterial, 3 arteriovenous)	12
Popliteal (44 arterial, 4 arteriovenous)	48
Tibial and Pedal (4 arterial, 1 arteriovenous, peroneal)	5
	<hr/>
Total	260

VASCULAR SURGERY

OPERATIONS FOR CONDITIONS OTHER THAN ANEURYSMS

Common Carotid	25
External Carotid and Branches	321
Axillary	4
External Iliac	1
Internal Iliac (4 bilateral)	8
Popliteal	1
	<hr/>
Total	360

RECAPITULATION

Operations for aneurysms, aneurysmal lesions and wounds	260
Operations for conditions other than aneurysms	360
	<hr/>
Total	620*

PART II

REGIONAL CLASSIFICATION IN DETAIL, WITH RESULTS

SURGERY OF THE CAROTID VESSELS

Operations upon Common Carotid (occlusions with aluminum bands, ligatures, sutures) for Aneurysms or Aneurysmal Conditions	
42 arterial aneurysms 24 proximal occlusions (cardiac side) 18 distal occlusions†	
11 arteriovenous aneurysms including 6 intracranial, carotid cavernous aneurysms 2 without exophthalmos, and 4 with exophthalmos	53
Operations upon Internal Carotid (band occlusions or ligatures)	
5 arterial aneurysms, including wound of middle cerebral	
2 arteriovenous intracranial aneurysms, without exophthalmos	7
Operations upon External Carotid and its Branches for Aneurysms or Aneurysmal Conditions (ligatures)	
4 arterial aneurysms	
7 arteriovenous aneurysms, including 2 intracranial aneurysms without exophthalmos	11
	<hr/>
Total operations for carotid aneurysms	71
Operations upon the Common Carotid (ligatures or band occlusions) for Non-aneurysmal Lesions	25
Operations upon the External Carotid and its Branches for Conditions other than Aneurysms (ligatures)	
90 ligations of external carotid trunk (including 8 bilateral ligations)	

* Since this list was completed (May 1, 1940), two more aneurysms have been added. Both popliteals. One a traumatic, arteriovenous, treated by excision and quadruple ligation, with complete recovery and perfect functional result, and one arterial, atheromatous. Obliterative endo-aneurysmorrhaphy complicated by popliteal thrombosis. Recovery, with amputation of foot.

† Distal occlusions chiefly on the Brasdor-Gunard principle for innominate and ascending aortic aneurysms involving origin of innominate. In these cases, the common carotid and right subclavian were ligated at the same, or more often at separate sittings, always beginning with the common carotid first, and applying a *removable* aluminum band (Matas-Allen type), to test the efficiency of the collateral circulation in the brain. For history and technic of these bands, see bibliography Nos. 23, 25, 28, 34, 44, 83 and 97.

34 ligations of individual branches of the external carotid in 34 of the above 90 ligations	
197 thyroid ligations preliminary to thyroidectomies	321
Total carotid operations for nonaneurysmal conditions	346

RECAPITULATION

Total carotid operations for aneurysms	71
Total carotid operations for conditions other than aneurysms	346
Total carotid operations for all causes	417*

REMARKS—As shown in the preceding tables, the occlusions of the common carotid (by bands or ligatures) for aneurysms amount to 53 cases. In addition to this, there are 25 common carotid occlusions for nonaneurysmal conditions, making a total of 78 common carotid ligations for all causes. If to these 78 common carotid ligations we add seven ligations of the internal carotid for aneurysm, the combined ligations of the common (78) and the internal carotid (seven) will amount to a total of 85 band occlusions or ligations of the two main carotid trunks for all causes, exclusive of 101 ligations of the external carotid for all causes, and 231 ligations of the external carotid branches.

SURGERY OF THE COMMON CAROTID

Proximal Occlusions

For arterial aneurysms

- 20 bands, with one death from cerebral complications in four days†
- 4 ligations, no deaths

For arteriovenous aneurysms

- 8 bands, with one death in nine days of heart complications (angina)
(One patient with cerebral symptoms was rescued by timely removal of band
and later cured by band after long periods of compression)
- 2 transvenous sutures, with one death in six days, of angina¹
- 1 intrasaccular suture, cured

35 Total proximal occlusions, with two deaths Mortality 2/35, or 5.7 per cent

¹ Same patient

Distal Occlusions (on the Brasdor-Guinard procedure for innominate and aortic aneurysms) all arterial

- 14 bands, no operative deaths‡
- 4 ligations, no operative deaths¶

18 Total distal occlusions, no operative deaths

* Ref bibliography Nos 19 (carotids), 23, 28, 41 and 44

† One patient died suddenly at his home, two months after band occlusion of common carotid, of hemorrhage from rupture of retropharyngeal abscess causing erosion and infection of old aneurysmal sac

‡ Two patients died of progressive tracheal compression from aneurysm, each about three weeks after distal occlusion of common carotid

¶ While attempting to perform a sternal resection to expose aneurysm, 19 days after distal ligation of common carotid, one patient died of laryngeal spasm, under ether

Operations upon the Common Carotid or Conditions other than Aneurysm
 12 bands, all with operative recovery (Two patients with cerebral symptoms were saved by timely removal of band)
 8 ligations, with three deaths from cerebral complications
 5 excisions of artery with tumor, with one death from cerebral complications

25 Total, with four deaths Mortality, 4 25, or 16 per cent

TYPES OF OPERATION IN SURGERY OF THE COMMON CAROTID

Bands

40 proximal occlusions with bands, (three deaths)
 20 for arterial aneurysms
 8 for arteriovenous aneurysms
 12 for conditions other than aneurysms
 14 distal occlusions with bands, no operative deaths 54

Ligatures

4 proximal ligations for aneurysms, no deaths
 8 proximal ligations for conditions other than aneurysm, three deaths
 4 distal ligations, no operative deaths 16

Suture Methods No operative deaths

2 transvenous sutures for arteriovenous aneurysms
 1 intrasaccular suture for arteriovenous aneurysm 3

Excisions

5 for conditions other than aneurysms, one death 5

Total 78

SURGERY OF THE INTERNAL CAROTID *

3 bands to internal carotid for arterial aneurysms
 1 for aneurysm of internal carotid
 1 for subclavian aneurysm (test bands), as precaution before ligating the innominate
 1 for aneurysm of left common carotid at bifurcation Death two days later, in spite of removal of band on appearance of cerebral signs, 18 hours after occlusion
 3 ligations, one for arterial aneurysm and two for arteriovenous aneurysms, of internal carotid, in all of which bands to common carotid had failed to cure the aneurysm No deaths
 1 emergency hemostatic intracranial control (middle cerebral) by forceps Death of preoperative hemorrhage and shock

7 Total occlusions of internal carotid, with two deaths Mortality, 2 7, or 28 5 per cent

REMARKS —In addition to the above, two arterial extracranial aneurysms of the internal carotid were cured by bands placed upon the common carotid, making in all a total of seven aneurysms of the internal carotid, of which four followed tonsillectomies or tonsillar abscesses

A summary of intracranial aneurysms follows, the operated cases also appearing previously in their respective tables

* Ref bibliography Nos 88, 91 and 97

INTRACRANIAL ARTERIOVENOUS FISTULAE OF THE CAROTID TRACT*

I Extracranial bands on the common carotid for intracranial arteriovenous fistulae without exophthalmos	2
II Ligations of the internal carotid for intracranial arteriovenous fistulae without exophthalmos after failure of common carotid ligations	2
III Extracranial bands on the common carotid for carotid-cavernous aneurysms (pulsating exophthalmos)	4
IV Previous ligations of the common carotid for pulsating exophthalmos followed by relapse and ultimate cure by spontaneous thrombosis	2
V Case of spontaneous carotid-cavernous arteriovenous aneurysm (pulsating exophthalmos) cured by spontaneous thrombosis without operation	1
VI Cases of intracranial arteriovenous communication (2 with exophthalmos, 2 without exophthalmos), in which for various reasons no operation was performed, and treatment limited to systematic carotid compression	4

TOTAL (not including cases observed and treated with colleagues) 15

SURGERY OF THE EXTERNAL CAROTID AND ITS BRANCHES†

Operations upon the External Carotid and Its Branches for Aneurysms or Aneurysmal Lesions

Arterial (no deaths)

3 ligations, 1 of the external carotid and 2 of the meningeal media

1 excision of arterial varix (scalp)

Arteriovenous (no deaths)

5 ligations, 3 for cavernous angiomas of the scalp and ear

1 obliterative endo-aneurysmorrhaphy

1 quadruple ligation

11 Total, all cured

Operations upon the External Carotid and its Branches for Conditions other than Aneurysms (mainly malignant growths of the jaws, mouth, neck, etc.)

90 ligations with seven deaths Mortality, 7.8, or 7.7 per cent

34 of the above 90 cases in which the branches of the external carotid were separately ligated

197 thyroid ligations

321 Total

REMARKS —From the above table it will be seen that I have recorded 101 ligations of the external carotid, of which 11 were ligations for aneurysms and aneurysmal conditions in the area of the external carotid distribution, all followed by recovery without cerebral complications

In addition to these 11 ligations, there are 90 ligations of the external carotid for surgical conditions other than aneurysms, included in this were eight bilateral ligations of the external carotid preliminary to operation for very extensive malignant disease. In the majority of cases the external carotid and its main branches were ligated together with the main trunk, or this, in a few instances, was injected with paraffin following the Dawson pro-

* Ref bibliography Nos 83, 88, and 97

† Ref bibliography, No 19, aneurysms of special arteries (carotids)

cedure, to obtain as complete an occlusion or obliteration of the external carotid tract as possible

These 90 ligations of the external carotid were followed in nine cases by postoperative complications which proved fatal in seven patients. The postoperative complications are classified as follows: Cerebral, five, pulmonary, three, cardiopulmonary, with a question mark (supposed to have been cerebral, but autopsy proved negative for cerebral lesions), one

Of the five cases in which the cerebral complications (stupor, contralateral hemiplegia, aphasia, coma) followed the ligation of the external carotid, three proved fatal and two recovered. But of these five cases of cerebral complications, only three can be clearly and positively attributed to the ligation of the external carotid. In the other two, one of the patients (age 55, resection of right upper jaw for sarcoma) had undergone the ligation of the external carotid without cerebral disturbances until the ninth day, when secondary hemorrhage compelled the ligation of the common carotid by the resident house surgeon. This was followed promptly by stupor, hemiplegia and aphasia from which the patient finally recovered, with seeming cure also of the disease. The other patient (age 44, bilateral ligation of the external carotid preliminary to excision of the tongue for extensive carcinoma with multiple, diffuse, secondary lymph node metastases in the submaxillary regions and neck) was operated upon in two stages. The last operation on the nodes was followed by aphasia and other signs of a right-sided block of the internal carotid, two weeks after the bilateral ligation of the external. The cerebral signs coincided with a purulent infection in the submaxillary wound. Despite this, the patient gradually recovered from the operation, the brain symptoms clearing completely after a few months. The patient died nevertheless, three years later, from generalized cervical and mediastinal metastases.

It would seem from this, that our experience in the ligation of the external carotid for nonaneurysmal causes were followed by cerebral complications in three cases, two of which proved fatal, thus establishing an incidence of cerebral complications in the nonaneurysmal group of 3.90, or 3.3 per cent, and a fatality of 2.90 or 2.2 per cent, or a death rate of 2.3, or 66.6 per cent of the brain complications.

If the 11 ligations for aneurysmal conditions are added to the 90 ligations for nonaneurysmal causes, equaling in all a total of 101 ligations, the incidence of the cerebral complications after this special ligation would be reduced to 2.97 per cent, and the mortality from cerebral complications would be reduced to 1.99 per cent.

From this we gather that the ligation of the external carotid must continue to be regarded as a relatively benign ligation, especially when compared with the dangers of the internal and common carotid ligations. None the less, an incidence of 3 per cent cerebral complications makes us regard the ligation of the external carotid as an added risk to whatever other dangers may be inherent in the operation for which the ligation is performed, and

this risk, minimal as it is, must weigh against the benefits that are expected to accrue from the ligation. I would say that, personally, I would not allow this possible risk to outweigh the positive and, undoubtedly, great hemostatic advantages that the preliminary ligation of the external carotid affords in controlling the vascular areas involved in the field supplied by these arteries.

Danger of Thrombus at the Bifurcation—When the first death from a preliminary ligation of the external carotid (ligation of the external carotid preliminary to excision of the second and third divisions of the trigeminus at the basal foramina, employing Mixter's modification of Salzer's method) occurred in my practice in 1893, I was very much impressed with the danger of a ligation close to the bifurcation, and believed that a thrombus, starting at the ligation and extending to the bifurcation, would in all probability break off at the tip to be swept away to the brain by the force of the carotid stream. I still believe this is possible, and perhaps probable, as long as the internal carotid is pervious. Once the internal carotid is firmly plugged by the clot, the possibility of embolism ceases as the arterial pressure will drop beyond the obstruction, and the carotid stream will be reversed from the brain to the seat of the obstruction making it impossible for any emboli to float to the circle of Willis, though it is possible, as has been demonstrated by postmortem evidence, that a thrombus or clot may extend all the way from the bifurcation (after internal carotid ligations) to the level of the cavernous sinus in the internal carotid.

After my first experience I always ligated the external carotid as far as possible from the bifurcation, consistently with the hemostatic or denutrient purpose of the ligation. When the superior thyroid originated close to the bifurcation, I ligated the thyroid at its origin and the external carotid beyond this point. The very frequent anomalies in the origin of the anterior and ascending branches of the external carotid compelled variations in the ligation of the parent trunk and its branches in my efforts to keep at a respectable distance from the bifurcation. My experience shows that, despite these anatomic precautions, cerebral ischemia may occur with or without a detached embolus. None the less, it is rational to ligate as far as possible beyond the bifurcation. In any case, it would seem that the thrombus must precede the embolus, if this is ever detached, before the internal carotid has been completely plugged.

SURGERY OF THE INNOMINATE*

6 provisional ligations for hemostatic control during operations for subclavian aneurysms (no deaths)

2 arterial

4 arteriovenous

4 permanent occlusions of the innominate with bands or ligatures (3 bands, 1 ligation, all arterial)

There were two deaths, one from pulmonary complications and hemorrhage on

* Ref bibliography Nos 19 (section on aneurysms of special arteries, innominate), 71 and 83

the sixth day after band occlusion, another (ligation) from consecutive secondary hemorrhage and cerebral complications from infected gunshot wound of the carotid

- 3 innominate aneurysms wired with Colt's apparatus, with notable effect on the aneurysms and marked symptomatic relief In these cases wiring followed distal ligation of the common carotid and third right subclavian as a precaution against cerebral embolism

13 Total, with two deaths Mortality, 2 13, or 15 3 per cent

SURGERY OF THE SUBCLAVIAN*

Operations upon the Subclavians for Arterial Aneurysms (no deaths)

- 12 proximal bands or ligations for subclavian aneurysms
 - Right subclavian, 3 bands, 2 ligations
 - Left subclavian, 3 bands, 4 ligations
- 2 ligations of third subclavian for axillary traumatic (pulsating) hematomata
 - Right subclavian, cured
 - Left subclavian, died of preoperative shock and hemorrhage
- 11 distal occlusions of the third subclavian for innominate and aortic aneurysms, 8 bands, 3 ligations (no deaths)

Operations upon the Subclavians for Wounds

- 2 for subclavian wounds
 - 1 clamping for wound of inferior thyroid in extirpating metastatic carcinoma of the larynx and thyroid (Died third day from shock, surgical anemia and hypostatic pneumonia)
 - 1 excision of cervical rib and segment of blocked artery for thrombotic occlusion of left subclavian artery
- 2 for wounds of subclavian branches
 - 1 traumatic (bullet wound) aneurysm of vertebral artery, direct intervention by aneurysmotomy and packing vertebral canal, cured
 - 1 emergency hemostasis of internal mammary (with clamp) for stab wound of internal mammary causing fatal hemothorax, died

29 Total operations on subclavian artery and branches, three deaths Mortality, 3 29, or 6 9 per cent

Operations upon the Subclavians for Arteriovenous Aneurysms

- 6 direct operations
 - Right subclavian, 4 ligations, no deaths In one of these, the dilated subclavian artery was ligated to control an arteriovenous angioma of the arm
 - Left subclavian, 1 band and 1 transvenous suture, no deaths
- 1 ligation of thyroid axis and branches for arteriovenous aneurysm after provisional ligation of innominate, cured

7 Total operations upon the subclavian for arteriovenous aneurysms, no deaths

RECAPITULATION

- 29 operations upon subclavians, arterial
- 7 operations upon subclavians, arteriovenous

36 Total subclavian operations, with three deaths Mortality, 3 36, or 8 2 per cent

* Ref bibliography Nos 8, 19, 62 and 78

SURGERY OF AXILLARY VESSELS*

Axillary Surgery for Arterial Aneurysm

- 1 axillary arterial aneurysm was cured by double ligation of the artery at the seat of injury (In two others the third subclavian was ligated)

Axillary Surgery for Arteriovenous Aneurysms

- 3 axillary arteriovenous aneurysms were cured, two by transvenous suture and one by quadruple ligation with excision

Axillary Surgery for Conditions other than Aneurysms

- 4 injuries in the course of radical extirpation of malignant growths
 - 2 ligations
 - 1 circular suture
 - 1 lateral suture

8 Total, no deaths

SURGERY FOR ANEURYSMS OF THE BRACHIAL AND ITS BRANCHES, INCLUDING ANEURYSMS AND WOUNDS OF THE HAND†

Brachial Aneurysms

- 3 arterial, all cured
 - 1 intrasaccular suture
 - 2 obliterative endo-aneurysmorrhaphies
- 2 arteriovenous, all cured
 - 1 transvenous suture
 - 1 quadruple ligation

5 Total, no deaths

Note One brachial, not operated upon, was spontaneously cured

Radial Aneurysms

- 3 arterial, all cured
 - 1 obliterative endo-aneurysmorrhaphy
 - 2 restorative endo-aneurysmorrhaphies

3 Total, no deaths

Aneurysms and Wounds of the Hand

- 1 arteriovenous cavernous angioma of the hand, cured by excision
- 1 arteriovenous wound cured by occlusion with clamp

2 Total, no deaths

SURGERY OF THE ABDOMINAL AORTA

- 1 pathogenic (nonsyphilitic) in white male, age 23, involving abdominal aorta in proximity to celiac axis Treated by various methods including celiotomy and peritoneal isolation of sac, secondary wiring and electrolysis (Moore-Corradi method) Temporary improvement Death from subperitoneal rupture 54 days after operation‡
- 1 colored female, age 28, syphilitic, ruptured aneurysm of the bifurcation, including both common iliac arteries, ligation of abdominal aorta with double cotton tape ligatures Death from fulminating pulmonary hemorrhage, one year, five months and nine days after the ligation, with aneurysm clinically and anatomically cured¶

* Ref bibliography Nos 19, 41, and 44

† Ref bibliography Nos 1, 5, 32, 52 and 55

‡ For discussion ref bibliography Nos 7, 9, 19 and 29

¶ Ref bibliography Nos 53, 62 and 104

- 2 abdominal aortic aneurysms treated by exploratory celiotomy and Colt's wire wisps, all operative recoveries with seeming temporary improvement *
- 1 exploratory celiotomy, aneurysm in upper aorta exposed, no safe place could be exposed to wire Abdomen closed without wiring Death 25 hours after operation from rupture of the sac and fulminating hemorrhage into left pleural cavity *
- 2 exploratory celiotomies for suspected aortic aneurysms, no aneurysms found, other pathology corrected, patient cured *

7 Total, no deaths attributable to operation

SURGERY OF THE EXTERNAL, COMMON AND INTERNAL ILIACS†

Arterial Aneurysms

- 1 obliterative endo-aneurysmorrhaphy, aneurysm involving the common and external iliacs, cured
- 2 bands to external iliac for aneurysms of the external iliac, both cured

3 Total, no deaths

Note A case of bilateral aneurysms of the common iliac was cured by ligation of the abdominal aorta, and is tabulated under abdominal aorta

Arteriovenous Aneurysm

- 1 transvenous suture for aneurysm of external iliac, died on third day after operation, from gangrene of a loop of ileum

Conditions other than Aneurysms

- 1 iliac ligation and resection for femoral tubercular adenitis Gangrene of foot and leg on third day, amputation, death four weeks after operation, following gradual decline
- 8 (4 bilateral) ligations of internal iliac as prophylactic hemostatic as first step of a Wertheim operation for malignancy of uterus, all operative recoveries

13 Total, with two deaths Mortality, 2 13, or 15 3 per cent

SURGERY FOR ILIOFEMORAL ANEURYSMS‡

Iliofemoral Arterial Aneurysms

- 12 bands to external iliac (one relapse cured by obliterative endo-aneurysmorrhaphy), all cured
- 1 obliterative endo-aneurysmorrhaphy (following relapse from band), cured
- 1 ligation of external iliac, died on seventh day from surgical anemia and exhaustion

14 Total, with one death

Iliofemoral Arteriovenous Aneurysms

- 2 transvenous sutures, one cured, one died
- 1 ligation of common iliac, attempted quadruple ligation, died
- 1 quadruple ligation, cured

4 Total, two deaths

18 Total iliofemoral aneurysms operated upon, with three deaths Mortality, 3 18, or 16 6 per cent

* The details of these cases are given in the author's tables of individual records, previously referred to

† Ref bibliography Nos 19 (special aneurysms), 28, 41, 49 and 83

‡ Ref bibliography Nos 32, 34, 40, 44 and 45

FEMORAL SURGERY^{*}

Femoral Arterial Aneurysms

- 9 obliterative endo-aneurysmorrhaphies, all cured
- 1 reconstructive endo-aneurysmorrhaphy, cured
- 2 ligations in wound, no sac, both cured
- 2 intrasaccular ligations (in sac), both cured

14 Total, no deaths

Femoral Arteriovenous Aneurysms

- 9 restorative operations
 - 4 by detachment of anastomosis and preservation of both vessels by lateral angiorraphy, all cured
 - 1 by transvenous closure of fistula (transvenous arteriorraphy) with preservation of both artery and vein (in large varicose sac), cured
 - 4 by transvenous closure of fistula with preservation of artery and sacrifice of vein, all cured
- 8 obliterative operations
 - 2 obliterative endo-aneurysmorrhaphies by suture of all openings in a common sac, both cured
 - 6 quadruple ligations, with division of the vessels at the anastomosis, all cured
 - 1 irregular emergency procedure—hemostasis by hemostats left *in situ*, patient died

18 Total, one death, or 5.55 per cent mortality

32 operations for femoral aneurysms, with one death Mortality, 1/32 or 3.1 per cent

FEMOROPOPLITEAL SURGERY

Femoropopliteal Arterial Aneurysms

- 7 obliterative endo-aneurysmorrhaphies, all cured
- 1 reconstructive endo-aneurysmorrhaphy, cured
- 1 intrasaccular ligation (in sac)—died 24 hours following operation from preoperative anemia, shock and exhaustion, despite preliminary intravenous infusion and continued infusion during the operation

9 Total, one death Mortality, 1/9, or 11.1 per cent

Femoropopliteal Arteriovenous Aneurysms

- 3 obliterative operations
 - 2 obliterative endo-aneurysmorrhaphies, by suture of all openings in a common sac, cured
 - 1 quadruple ligation, with division of the vessels at the anastomosis, cured

3 Total, no deaths

12 femoropopliteal aneurysms operated upon, with one death Mortality, 1/12, or 8.33 per cent

POPLITEAL SURGERY[†]

Popliteal Arterial Aneurysms

- 37 obliterative endo-aneurysmorrhaphies, 35 cured, two died
- 1 restorative endo-aneurysmorrhaphy, cured
- 2 reconstructive endo-aneurysmorrhaphies, both cured
- 2 cured by mechanical compression

42 Total, two deaths Mortality, 2/42, or 4.76 per cent

^{*} Ref bibliography Nos 19, 32, 35, 41, 47 and 48

[†] Ref bibliography Nos 19, 32, 41, 47 and 48

Popliteal Arterial Injuries

2 amputations for popliteal injuries, gangrenous on admission Recovery

Popliteal Arteriovenous Aneurysms

3 quadruple ligations, with partial excision of sac, all cured

1 obliterative transvenous endo-aneurysmorrhaphy, cured

4 Total, no deaths

Conditions other than Aneurysms

1 bivascular circular angiography following excision of popliteal vessels for myxosarcoma, complicated by thrombosis at anastomosis, final recovery with amputation six months after bivascular anastomosis

49 Total operations upon popliteal vessels, with two deaths Mortality, 2 49, or 4 0 per cent

TIBIAL AND PEDAL SURGERY¹

Tibial and Pedal Arterial Aneurysms

2 restorative endo-aneurysmorrhaphies

1 tibial, cured

1 dorsalis pedis, cured

1 obliterative endo-aneurysmorrhaphy High bivascular, tibial, cured

1 reconstructive endo-aneurysmorrhaphy, tibial, cured

Peroneal Arteriovenous Aneurysm

1 restorative endo-aneurysmorrhaphy, cured

5 Total, no deaths

Note There were no deaths and no gangrene in this group Suture methods were employed in all, there were no ligations except in two other tibial wounds not included in the above cases—cases of fresh tibial wounds, both healing perfectly

PART III

SUMMARY OF PROCEDURES EMPLOYED BY DOCTOR MATAS IN SIX HUNDRED AND TWENTY OPERATIONS UPON THE BLOOD VESSELS, FOR ALL CAUSES, FROM 1888-1940

Suture Methods

68 obliterative endo-aneurysmorrhaphies (for aneurysms)

25 restorative endo-aneurysmorrhaphies (for aneurysms)

5 reconstructive endo-aneurysmorrhaphies (for aneurysms)

1 circular angiography (popliteal), following excision for myxosarcoma

2 sutures of axillary wounds (radical extirpation of malignancies)

101 Total operations by suture methods, for all causes

Occlusions with Bands, Ligatures, and other Methods

89 bands (77 for aneurysms, 12 for conditions other than aneurysms)

402 ligations

47 single ligations for aneurysms

15 quadruple ligations for arteriovenous aneurysms

340 for conditions other than aneurysms

8 excisions (three for aneurysms, five for conditions other than aneurysms)

6 wirings for aneurysms

3 exploratory celiotomies, for aneurysms, no wiring

* Ref bibliography No 52

5 clappings for aneurysms and wounds

1 aneurysmotomy and plugging orifices of wounded artery in vertebral canal for aneurysm

1 intrasaccular ligation for aneurysm

2 mechanical compressions (popliteal)

2 amputations for popliteal injuries, gangrenous on admission

519 Total occlusion with bands, ligatures, and other methods for all causes

RECAPITULATION

101 operations by suture methods

519 operations by methods of ligation (including aluminum bands)

620 Total operations

PROCEDURES EMPLOYED BY DOCTOR MATAS IN SIX HUNDRED AND TWENTY OPERATIONS UPON THE BLOOD VESSELS, FOR ALL CAUSES, FROM 1888-1940

SUTURE METHODS

68 Obliterative Endo-aneurysmorrhaphies (Matas), All for Aneurysms

Arterial

3 brachial, cured

1 radial, cured

1 external iliac and common iliac, cured

1 iliofemoral, cured following relapse six months after band to external iliac

11 femoral, cured

7 femoropopliteal, all cured

37 popliteal (10 high popliteal, all cured, 20 midpopliteal, 18 cured, two died, seven low popliteal, all cured)

1 tibial, high bivascular, cured

Arteriovenous

1 common carotid, cured with preservation of artery and sacrifice of vein

1 left temporal branch of external carotid, cured

2 femoral, all openings sutured in a common sac, both cured

2 femoropopliteal, cured

68 Total, with two deaths Mortality, 2 68, or 2 9 per cent

30 Restorative Operations, All for Aneurysms

5 reconstructive endo-aneurysmorrhaphies (all arterial)

1 femoral, cured

1 femoropopliteal, cured

2 popliteal, both cured

1 tibial, cured

10 restorative endo-aneurysmorrhaphies (Matas)

Arterial

2 radial, cured

1 popliteal, cured

1 tibial, cured

1 dorsalis pedis, cured

Arteriovenous

4 femoral, all cured (Detachment of anastomosis and preservation of both vessels by lateral angiorraphy)

1 peroneal, cured

15 restorative endo-aneurysmorrhaphies (Matas-Bickham operation by transvenous suture)

VASCULAR SURGERY

- 2 common carotid, with preservation of artery and sacrifice of vein One cured One case, transvenous suture following relapse from band to common carotid, sudden death in one week of preexisting coronary disease
- 1 left subclavian, cured, with preservation of artery and sacrifice of vein
- 2 axillary, both cured, with preservation of artery and sacrifice of vein
- 1 brachial, cured, with preservation of artery and sacrifice of vein
- 1 external iliac, preservation of both artery and vein Died from thrombosis of mesentery
- 2 iliofemoral, preservation of both artery and vein One cured, one died on eighth day of erysipelas and fatal septic, thrombophlebitic pyemia
- 5 femoral, all cured, one with preservation of both artery and vein, and four with preservation of artery and sacrifice of vein
- 1 popliteal, cured

-
- 30 Total, with three deaths Mortality, 3 30, or 10 per cent
- 1 bivascular circular angiography (popliteal), following excision for myxosarcoma Recovery
 - 2 sutures of axillary wounds (injuries in the course of radical extirpations of malignant growths) Recovery

RECAPITULATION

SUTURE METHODS

- 68 endo-aneurysmorrhaphies, obliteratives, with two deaths
- 25 restorative endo-aneurysmorrhaphies, with three deaths
- 5 reconstructive endo-aneurysmorrhaphies, all cured
- 1 bivascular circular angiography, with recovery
- 2 sutures of axillary wounds, with recovery

-
- 101 Total, with five deaths Mortality, 5 101, or 4 9 per cent

RECAPITULATION—ENDO-ANERYSMORRAPHIES

- 98 Total Endo-aneurysmorrhaphies
 - 68 oblitative, 68 98, or 69 22 per cent
 - 25 restorative, 25 98, or 26 52 per cent
 - 5 reconstructive, 5 98, or 5 10 per cent

98 Total endo-aneurysmorrhaphies, with five deaths

Remarks If we subtract three deaths due to extrinsic causes (one from coronary disease, one from thrombosis of mesentery, and one from erysipelas) we have a mortality of 2 98, or 2 4 per cent

OCCCLUSIONS WITH BANDS, LIGATURES, AND OTHER METHODS

- 89 Occlusions with Bands
 - 68 bands for arterial aneurysms
 - 20 proximal common carotid, with one death
 - 14 distal common carotid, with no operative deaths
 - 3 internal carotid, one death
 - 3 innominate, one death
 - 6 proximal subclavian, no deaths
 - 8 distal subclavian, no deaths
 - 14 external iliac and iliofemoral, no deaths
 - 9 bands for arteriovenous aneurysms

8 common carotid, no deaths (One death followed a second operation, trans-venous suture, but was caused by preexisting coronary disease)

1 subclavian, cured

12 bands for conditions other than aneurysm, no deaths

12 common carotid

89 Total band occlusions, with three deaths Mortality, 3.89, or 3.3 per cent

402 Occlusions with Ligatures

62 ligations for aneurysms

Arterial (single ligatures—silk, catgut, tendon, cotton tape)

4 proximal common carotid, no deaths

4 distal common carotid, no deaths

1 internal carotid, cured

3 external carotid (two meningeal media), all cured

2 provisional innominate ligations, no deaths

1 permanent innominate ligation, with death from consecutive secondary hemorrhage and cerebral complications from infected gunshot wound of the carotid

11 subclavian

6 proximal, two right, four left, all cured

2 third subclavian for axillary traumatic (pulsating) hematoma, one right, cured, one left, died of preoperative hemorrhage and shock

3 distal, no deaths

1 axillary, cured

1 abdominal aorta, cured

1 external iliac, died on seventh day from surgical anemia and exhaustion

2 femoral ligations in wounds, no sac, cured

Arteriovenous (single ligatures)

2 internal carotid, cured

5 external carotid (three for cavernous angioma of the scalp and ear) all cured

4 provisional innominate, no deaths

5 subclavian

4 right, cured

1 thyroid axis and branches, cured

Arteriovenous (quadruple ligatures)

1 external carotid, cured

1 axillary, cured

1 brachial, cured

2 iliofemoral, one cured, one attempted quadruple ligation, died same day of hemorrhage and shock

6 femoral, all cured

1 femoropopliteal, cured

3 popliteal, with partial excision of sac, all cured

62 Total ligations for aneurysms, with four deaths Mortality, 4.62, or 6.4 per cent

340 Ligations for Conditions other than Aneurysm

8 proximal ligations of the common carotid, mainly for malignant growths
Three deaths from cerebral complications

90 ligations of the external carotid, mainly for malignant growths with seven deaths (cerebral, three, pulmonary, three, cardiopulmonary, with a question mark, one)

34 ligations of branches separately ligated at time of external carotid ligation

- 197 ligations of thyroid arteries, either as a preliminary to operation or in the course of operation for thyroid disease (One death from laryngeal spasm)
 - 2 ligations of axillary arteries for injuries during the course of radical extirpation of malignant growths Recovery
 - 1 iliac ligation for tuberculous adenitis, thrombotic occlusion, gangrene of leg, amputation, final death four weeks after ligation
 - 8 ligations of internal iliac in four bilateral ligations as a prophylactic hemostatic, as first step of a Wertheim operation for malignancy of uterus No deaths
-
- 340 Total ligations for conditions other than aneurysms, twelve deaths Mortality 12 340, or 3.5 per cent
 - 402 total ligations for all causes, with sixteen deaths Mortality, 16 402, or 3.9 per cent
 - 8 excisions or extirpations
 - Arterial
 - 1 external carotid, excision of arterial varix, cured
 - 1 subclavian, excision of cervical rib for thrombotic occlusion and of blocked segment of left subclavian, cured
 - Arteriovenous
 - 1 excision of cavernous (arteriovenous) metastatic angioma of chest, cured
 - Conditions other than aneurysm
 - 5 excisions of common carotid with tumor, four recovered, one died
 - 6 Wiring
 - Arterial aneurysms
 - 3 innominate-aortic, recovered from operation with variable periods of improvement and survival
 - 3 abdominal-aortic, recovered from operation with variable periods of improvement and survival
 - 3 exploratory celiotomies for abdominal aneurysms (no wiring)
 - 2 cases, other pathology found and cured
 - 1 (no safe place to wire) patient died in 25 hours from rupture of aneurysm
 - 5 clamping
 - Arterial wounds
 - 1 wound of inferior thyroid, emergency hemostasis by clamping subclavian, died third day from shock, surgical anemia and hypostatic pneumonia
 - 1 emergency hemostasis of internal mammary (with clamp) for stab wound causing fatal hemothorax
 - 1 intracranial control by forceps of middle cerebral for gunshot wound, death from preoperative hemorrhage and shock
 - Arteriovenous wounds
 - 1 wound of palmar arch, cured by occlusion with clamp
 - 1 wound of femoral vessels, hemostats (clamps) left *in situ*, death
 - 1 aneurysmotomy and plugging orifices of bleeding artery in vertebral canal
 - 1 aneurysm of vertebral artery, cured
 - 1 intrasaccular ligation (in sac)
 - 1 femoropopliteal Died 24 hours following intrasaccular ligation from preoperative anemia, shock and exhaustion, despite preliminary intravenous infusion and continued infusion during the operation
 - 2 mechanical compression
 - 2 popliteal aneurysms cured by proximal mechanical compression
 - 2 amputations
 - 2 amputations for popliteal artery injuries, gangrenous on admission Both recovered, with aneurysm cured

RECAPITULATION

METHODS OF OCCLUSION, INCLUDING LIGATURE, BANDS AND CLAMPS

- 89 bands, three deaths
- 402 ligations, 16 deaths
 - 8 excisions of aneurysms and segments of vessels, one death
 - 6 wirings for arterial aneurysms, no operative deaths
 - 3 exploratory celiotomies for aortic aneurysms, no operative deaths
 - 5 clampings, four deaths—emergency hemostasis of large arteries
 - 1 aneurysmotomy and plugging bleeding orifices of vertebral aneurysm, cured
 - 1 intrasaccular ligation, died (Annandale procedure)
 - 2 mechanical compressions for aneurysm, cured (Matas' calipers compressor)
 - 2 amputations for ruptured popliteal aneurysm—gangrene before operation, no deaths

519 Total occlusions, with 25 deaths Mortality 25 519, or 4.81 per cent
 101 operations by methods of suture, five deaths Mortality 5 101, or 4.9 per cent

GRAND TOTAL

620 operations, 30 deaths Mortality 30 620, or 4.83 per cent

CHRONOLOGIC BIBLIOGRAPHY

OF

CONTRIBUTIONS TO VASCULAR SURGERY

BY

RUDOLPH MATAS, M D , 1888-1940

- ¹ 1888—Traumatic Aneurysm of the Left Brachial Artery (illus) (First application of the intrasaccular suture) Med News, Phila, 53, 462-466, October 27, 1888
- ² 1891—Clinical Report on Intravenous Saline Infusion in the Charity Hospital, from June, 1888-1891 New Orleans Med and Surg Jour, 19, 1-33, 81-93, 1891 (Record of first intravenous infusion for shock and hemorrhage in New Orleans)
- ³ 1892—Large Cavernous Angioma Involving the Integument of an Entire Auricle Successfully Treated by Preliminary Ligation of the External Carotid Dissection, Free Resection of the Angiomatous Tissue and Ligation of the Afferent Trunks, *in situ*, by a Special Method of Hemostasis Med News, Phila, 61, 701-705, 1892
- ⁴ 1893—Traumatism and Traumatic Aneurysms of the Vertebral Artery and their Surgical Treatment, with Report of a Cured Case (Tables, illus) Address before Post-graduate School of Medicine, Chicago (1892) ANNALS OF SURGERY, 18, 477-521, 1893, Abst No Am Practitioner, 5, 503, 1893 Trans Pan-Amer Med Congress, 1, 624, Washington, 1895
- ⁵ 1894—Notes on Cases Illustrating Surgical Lesions of the Vascular System New Orleans Med and Surg Jour, 22, 241-265, 1894
- ⁶ 1897—Arterial Varix of the Lower Lip, Involving the Coronary Branches of the Facial Artery Extirpation under Cocaine Anesthesia Med News, Phila, 71, 207-208, 1897
- ⁷ 1900—Treatment of Abdominal Aortic Aneurysm by Wiring and Electrolysis Critical Study of the Moore-Corradi Method Based upon the Latest Clinical Data Trans So Surg Assn, 13, 272-330, 1900, Amer Med, 546-589, 1901
- ⁸ 1901—Traumatic Arteriovenous Aneurysm of the Subclavian Vessels With an Analytical Study of 17 Reported Cases, Including One Successfully Operated upon by the Author Trans Am Surg Assn, 19, 237-304, 1901, J A M A, 38, 103-107, 173-176, 318-324, 1902

- ⁹ 1901—Treatment of Aortic Aneurysm by Wiring and Electrolysis Trans Am Surg Assn, 19, 374, 1901 (Discussion following Dr Leonard Freeman's paper)
- ¹⁰ 1902—Operation for the Radical Cure of Aneurysm, Based upon Arteriorraphy (illus) Trans Am Surg Assn, 20, 396-434, 1902 ANNALS OF SURGERY, 37, 161-196, 1903 (This is the first systematic description of the author's operation of endo-aneurysmorraphy)
- ¹¹ 1902—Remarks on the Surgical Treatment of Aneurysms Proc Orleans Parish Med Soc, 97, 1902
- ¹² 1905—The Suture in the Surgery of the Vascular System Address before the Alabama State Medical Society Proc Ala State Med Soc, 243-270, 1905
- ¹³ 1905—Further Experience in the Radical Operation for the Cure of Aneurysm (By the author's method of intiasaccular suture (endo-aneurysmorraphy) Trans Am Surg Assn, 23, 323-388, 1905
- ¹⁴ 1906—Radical Cure of Aneurysm Present Status of the Method of Intrascacular Suture (Endo-aneurysmorraphy) Trans A M A, Surg Sect, Boston, 1906, J A M A, 47, 990-998, 1906
- ¹⁵ 1907—Pulmonary Embolism Trendelenburg's Procedure (Discussion at the meeting of South Surg and Gynec Assn, December 1907, Trans, pp 373-376, following paper of Doctors Bartlett and Thompson on "Mechanism and Clinic of Pulmonary Embolism")
- ¹⁶ 1908—Recent Advances in the Technic of Thoracotomy and Pericardiotomy for Wounds of the Heart (Remarks introductory to a series of demonstrations on the cadaver with the stereopticon at the meeting of the South Surg and Gynec Assn, Dec, 1907 Trans, 20, 175-186, South Med Jour, 1, 75-81, 1908)
- ¹⁷ 1908—Statistics of Endo-aneurysmorraphy or the Radical Cure of Aneurysm by Intrascacular Suture J A M A, 51, 1667-1671, 1908 Chairman's Address, Surgical Section, Chicago, 1908
- ¹⁸ 1909—Spontaneous Thrombosis of Cavernous Sinus Followed by Marked Improvement, in an Aggravated Pulsating Exophthalmos and Cirroid Aneurysm of 18 Years' Standing New Orleans M and S Jour, 61, 739-742, 1909
- ¹⁹ 1909—Surgery of the Vascular System A Treatise Embodied in Keen's Surgery 5, Chap 70, 1-350, 1909 (illus) Saunders and Co, Philadelphia (This treatise discusses comprehensively, the surgerv of the pericardium and heart, the diseases and injuries of the arteries, suture of arteries, veins, diseases and injuries, hemorrhage, the hemorrhagic diseases and their treatment, arterial aneurysms, arterio-venous aneurysms, and aneurysms of special arteries)
- ²⁰ 1910—Aids to Conservatism in Determining the Line of Amputation after Crushing and Other Mutilating Injuries of the Limbs (Hyperemia Reaction) The Military Surgeon, Chicago, 17, 131-145, 1910
- ²¹ 1910—Momburg's Method of Circular Elastic Aortic Compression (The author's original experiments and observations, with Dr John Smyth and Staff) Discussion, Trans Am Surg Assn, 28, 622-623, 1910
- ²² 1910—Omentopexy for Portal Obstruction (Narath's Operation) Trans South Surg and Gynec Assn, 23, 237, 1910
- ²³ 1910—Some of the Problems Related to the Surgery of the Vascular System Testing the Efficiency of the Collateral Circulation as a Preliminary to the Occlusion of the Great Surgical Arteries President's Address, Am Surg Assn Trans Am Surg Assn, 28, 4-54, 1910 (illus) (In this the author's original experiments and methods are fully described) ANNALS OF SURGERY, 53, 1-43, January, 1911
- ²⁴ 1910—Discussion on Bone Aneurysms (Following reading of Dr Bloodgood's paper on this subject) Trans Am Surg Assn, 32, 187, 1910
- ²⁵ 1910—Tests to Determine the Efficiency of the Collateral Circulation (Discussion before American Surgical Association, 1910) ANNALS OF SURGERY, 52, 126-130, 1910

- ²⁶ 1911—Foreign Bodies in the Pericardium and Heart, and Wounds of the Coronary Arteries (in Spanish) Clinica Moderna Zaragoza, 10, 411-418, 1911 Translated by Dr R Lozano
- ²⁷ 1911—Angiomata Blood Vessel Tumors Sajous' Cyc Med Sc, 7th ed 2, 502-546, 1911 (illus) F A Davis, Phila
- ²⁸ 1911—Occlusion of the Large Surgical Arteries with Removable Bands (Metallic) to Test the Efficiency of the Collateral Circulation (with Dr C A Allen) J A M A, 56, 232-239 (illus)
- ²⁹ 1911—Wiring of Aneurysms (Discussion of Dr Kirschner's paper on the "Matas Operation") Trans South Surg and Gynec Assn 24, 274-277, 1911
- ³⁰ 1913—Practicability of Reducing the Caliber of the Thoracic Aorta by Plication or In-folding of its Walls (with Dr C A Allen) (An experimental research) ANNALS OF SURGERY, 58, 304-319, 1913 (illus) Trans Am Surg Assn, 31, 193-217, 1913
- ³¹ 1913—Surgery of the Arterial System Abst Proc Internat Med Cong, London, August, 1913 J A M A, 61, 800, 1913
- ³² 1913—The Suture as Applied to the Surgical Cure of Aneurysm Trans 17th Internat Med Cong, London Sect 7, pt 2, 149-172, 1913 (Copiously illustrated with lantern slides) With remarks in closing the discussion
- ³³ 1913—Progress in the Surgery of the Vascular System Railway Surgeon, Chicago, 20, 136-139, 1913
- ³⁴ 1914—Testing the Efficiency of the Collateral Circulation as a Preliminary to the Occlusion of the Great Surgical Arteries J A M A, 63, 1446-1447, 1914 Trans A M A, Surg Sect, 366-412, 1914 (Critical review of progress)
- ³⁵ 1914—Vascular Clinic Case Reports
 - (1) Traumatic Arteriovenous Aneurysm of the Femoral Vessels at the Groin, Detachment and Separate Suture of the Vessels—Recovery
 - (2) Thrombotic Occlusion of Right Common Iliac Vein at about the Bifurcation of the Inferior Vena Cava
 - (3) Specimens of Anterior and Posterior Tibial Arteries in Diabetic Gangrene (Proc Touro Clinical Society) New Orleans M and S Jour, 66, 736-748, 1914
- ³⁶ 1915—Present Status of the Operation of Endo-aneurysmorrhaphy (Remarks in discussion of the paper by Dr H B Gessner) New Orleans M and S Jour, 67, 603-607, 1915
- ³⁷ 1916—Principles Governing the Surgical Treatment of Aneurysms (Mutter Lecture) Philadelphia, 1916 (Statistical and critical review of the vascular surgery of the World War, 1914-1916, chief data embodied in "Military Surgery of the Vascular System" Supplementary, 7, Keen's Surgery, 1921)
- ³⁸ 1916—Aneurysms of the heart (illus) Proc Touro Clinical Society, January, 1916 (unpublished)
- ³⁹ 1919—Endo-aneurysmorrhaphy I Statistics of the Operation II Personal Experience and Observations on the Treatment of Arteriovenous Aneurysms by the Intrascacular Method of Suture With Special Reference to the Transvenous Route Trans So Surg Assn, 32, 447-450, 451-489, 1919
- ⁴⁰ 1920—Endo-aneurysmorrhaphy Statistics of the Operation Personal Experience and Observations Surg, Gynec and Obstet, 30, 547-549, 1920 (with remarks on nomenclature)
- ⁴¹ 1920—Some Experiences and Observations on the Treatment of Arteriovenous Aneurysms by the Intrascacular Method of Suture (Endo-aneurysmorrhaphy) With Special Reference to the Transvenous Route—A Summary In "Contributions to Medical and Biological Research (illus)" Dedicated to Sir William Osler in honor of his seventieth birthday, July 19, 1919 Hoeber, New York, 2, 1047-1094 Also in ANNALS OF SURGERY, 71, 403-427, 1919
- ⁴² 1920—Angioma and Lymphangioma Treated by the Author's Method of Adrenalin

- Ischemia and Sponge Scrub (Discussion following Doctor Reder of St Louis, at meeting of A M A , April, 1920) Trans , A M A , Surg Sect , 1920
- ⁴³ 1921—Routes of Access to the Heart Lessons Gathered from the Experience of the Late War Med Rec , New York, 99, 595-599, 620, 1921
- ⁴⁴ 1921—Military Surgery of the Vascular System Keen's Surgery Supplementary, 7, 713-819 Saunders, Philadelphia (Full review of cardiovascular surgery of the World War, 1914-1918)
- ⁴⁵ 1921—On the Systemic Effect of Arteriovenous Aneurysms of the Heart and Circulation (With introductory address on the life and character of John Thompson Hodgen) The first John Thompson Hodgen lecture Delivered before the St Louis Surgical Society, March 26, 1921 Subsequently enlarged and published in the Trans South Surg Assn , 36, and in the Internat Clin , 2, Series 35, 1925
- ⁴⁶ 1922—Resultats Immédiats et Eloignés de l'Anevrismorrhaphie Report by invitation to the Cong of the Association Franc de Chir , October 27, 1922, Paris Comptes-rendus 31, Cong d l'Assn d Chir 1922, 395-413 Abst Proc 31 Cong Assn Franc de Chir , Gaz d Hôpitaux, October, 1922
- ⁴⁷ 1922—Arteriovenous Fistula of Femoral Vessels Surg Clin N Am , 2, 1165-1188 (illus)
- ⁴⁸ 1923—Resultats Immédiats et Eloignés de la Cure des Aneurysmes Arteriels et Arterio-veineux par la Suture Intrasacculaire (l'endo-anevrismorrhaphie) Presse Med 31, 109-112 (original contribution)
- ⁴⁹ 1924—Congenital Arteriovenous Fistula Discussion of Dr W F Rienhoff's paper Meeting of A M A , June, 1924 (Manuscript received too late to appear in report of proceedings)
- ⁵⁰ 1924—Subclavian Arteriovenous Aneurysm Discussion of Doctor Reid's paper on personal experiences, quoted at meeting of A M A , June, 1924 (Unpublished)
- ⁵¹ 1924—Methods of Treating Aneurysms by Intrasaccular Suture (lantern slide lecture) Scientific exhibit, Motion Picture Theatre, A M A , Chicago, June 11, 1924
- ⁵² 1924—Observations de trois cas d'aneurysmes Arteriels Peripheriques de la Main et du Pied Gueris par la Suture Intrasacculaire Conservatrice (endo-anevrismorrhaphie Reparatrice) Contribution to the "Livre d'or," in honor of Professor Emile Forgue, Montpellier, November 6, 1924 Reprint 8°, 1-20, illus Masson et Cie, Paris
- ⁵³ 1924—Preliminary Report of a Ligation of the Abdominal Aorta Above the Bifurcation, for an Acute, Ruptured Syphilitic Aneurysm Involving the Origin of Both Common Iliacs (Survival of the patient one year, five months and nine days after the ligation) Death caused by fulminating pulmonary hemorrhage from a tuberculous cavity The aortic aneurysm completely obliterated by dense clot The cure had been clinically effected at the time of the fatal pulmonary hemorrhage Trans Am Surg Assn , 42, 603-615, 1924 ANNALS OF SURGERY, 81, 457-464, 1925 Abstracted and reviewed by Doctor Guimbellot, Presse Medicale (Revue des Journaux, 168, September 19, 1925, and by Dr M Strauss, Zentralorgan f d ges Chir , etc , 31, 611, 1925)
- ⁵⁴ 1924—Surgical Treatment of Chronic Valvular Diseases of the Heart Discussion of Doctor Cutler's paper Trans Am Surg Assn , 42, 175-179, 1924
- ⁵⁵ 1924—Aneurysms of the Palmer Arches Discussion of Doctor Lyle's paper Trans Am Surg Assn , 42, 677-679, 1924
- ⁵⁶ 1924—Endo-aneurysmorrhaphy Discussion of Doctor Gibson's and Doctor Porter's paper Trans Am Surg Assn , 42, 591-602, 625-637, 1924 (Unpublished)
- ⁵⁷ 1925—Branham's Syndrome in Arteriovenous Aneurysms (An example of the inseparable relation of scientific medicine and modern surgery) Proceedings Scientific Sectional Meeting, American College of Surgeons at Mobile, Ala, February 13-14, 1925 Published in abstract in program of meeting (Unpublished)
- ⁵⁸ 1925—Cardiovascular Effects of Arteriovenous Fistulae Clinical lecture at Charity Hospital, to the Members of the Southern Interurban Clinical Club of Internists

- Thirteenth Semi-annual Meeting, June 7, 1925 Demonstration of two cases of arteriovenous aneurysm (Unpublished)
- ⁵⁹ 1925—On the Immediate and End-results of the Cure of Arterial and Arteriovenous Aneurysms by the Method of Intrascapular Suture—Endo-aneurysmorrhaphy Lecture illustrated with numerous lantern slides, delivered by invitation of the Cincinnati Academy of Medicine, March 2, 1925 (No printed report)
- ⁶⁰ 1923—Inaugural Presidential Address with Remarks on Endo-aneurysmorrhaphy (Illustrated technic by moving films) Read before the Clinical Congress of American College of Surgeons, Philadelphia, October 28, 1925 Surg, Gynec and Obstet, 41, 701-705, 1925
- ⁶¹ 1926—Remarks on a Successful Ligation of the Abdominal Aorta, illustrated by a moving film, showing the case of Corinne Dunson, operated upon April 9, 1923, following a report of a "Ligation of Abdominal Aorta," by Dr Barney Brooks, at Dallas, Texas, meeting of the A M A, Surgical Section, April 21, 1926 (Unpublished)
- ⁶² 1926—Personal Experience in the Surgery of the Subclavian Vessels Paper read at the meeting of the Southern Surgical Association at Biloxi Miss, December 16, 1926 Trans South Surg Assn, 39, 213-227, 1926 Abstr, J A M A, 88, 595, 1927
- ⁶³ 1927—Address at the Inaugural Meeting of the Chirurgical Society of Barcelona, with moving picture illustrating Dr Matas' method of Endo-aneurysmorrhaphy for the Radical Cure of Aneurysm Ars Medica, Barcelona, November, 1927 (in Spanish)
- ⁶⁴ 1927—Illustrated stereopticon lecture on the "Surgical Treatment of Aneurysms" (with special reference to Dr Matas' method) before the Faculty and Student Body of the Medical School of Barcelona, October, 1927 (abstract in program, in Spanish)
- ⁶⁵ 1927—Tratamiento quirurgico de los Aneurismas por la Sutura Intrascapular (Ponencias y Conferencias), Jornadas Medicas de Madrid, 18-23 Octubre, 1927, 536-545 (in volume of transactions, Madrid, 1928) Lecture, by invitation, on the "Radical Cure of Aneurysm", illustrated by moving picture in the Assembly Hall of the University of Madrid during the Spanish Congress of Medicine, October, 1927 (see Trans of the Congress, Madrid, 1928)
- ⁶⁶ 1929—Endo-aneurysmorrhaphy (Obliterative Type) for Radical Cure of Aneurysm Remarks preliminary to a motion picture of the operation, as performed by the author at the Charity Hospital, on "Aneurysms of the Femoral, Popliteal and Tibial Arteries" Transactions seventeenth annual meeting Association of the Illinois Central Railroad System Surgical Journal of Chicago, 34, 215-218, 1929, and discussion
- ⁶⁷ 1929—The Cause and Mechanism of Postoperative Embolism Report presented at the Eighth International Congress of Surgery, Warsaw, July, 1929 (Rapports, 1, 137-144)
- ⁶⁸ 1930—Postoperative Thrombosis and Embolism The Present Status of the Question One of the three scientific addresses delivered in honor of Dr John Chalmers DaCosta on the "DaCosta Night" of the Philadelphia County Medical Society, April 30, 1930 Published in abstract in "The Roster," bulletin of the Society, April, 1930
- ⁶⁹ 1930—Editorial in the American Journal of Surgery for July, 1930, on "Postoperative Thrombosis and the Contributions of the Scandinavian Surgeons to the Surgery of Embolectomy"
- ⁷⁰ 1930—Discussion of Professor Gynar Nyström's paper on "Operative Relief of Pulmonary Embolism" Meeting of the American Surgical Association, Philadelphia, May 7, 1930 ANNALS OF SURGERY, 92, 528-530, 1930
- ⁷¹ 1931—A discussion of Dr A Storck's paper on the "Treatment of Aortic Aneurysms"

- by the Method of Jugulo-Carotid Anastomosis (Babcock's Operation) " New Orleans M and S Jour , 84, 448-454, 1931
- ⁷² 1931—On Autotransfusion Letter to the New Orleans M and S Jour , 84, 69-71, July, 1931 (establishing priority of W S Halsted, for this method of transfusion)
- ⁷³ 1932—Personal Experience in the Surgery of the Subclavians (illus with lantern slides) Address at Scientific Session and Dedication Exercises of the Medical Department, University of Texas, Galveston, Texas, May 30, 1932 (No printed proceedings)
- ⁷⁴ 1932—Personal Experiences in the Surgical Treatment of Aneurysms Proceed Am Surg Assn, New Haven, Conn, May 17, 1932, ANNALS OF SURGERY, 114, 802-839, November, 1940
- ⁷⁵ 1932—Discussion of Doctors Scott and Morton's paper on "The Treatment of Common Arterial Diseases of the Lower Extremities " J A M A , 99, 984-985, 1932 Meeting of A M A , New Orleans, May 13, 1932
- ⁷⁶ 1932—The Donald C Balfour Lecture, University of Toronto, April 5, 1932, on "Postoperative Thrombosis and Pulmonary Embolism, Before and After Lister A Retrospect and Prospect " Bull Med Faculty, University of Toronto, 1932 Reprint 8°, 32
- ⁷⁷ 1932—Cirsoid Aneurysm of the Face and Scalp Synopsis of an illustrated report of a recent operation for the radical cure of a traumatic arteriovenous aneurysm (cirsoid) involving the left half of scalp and left parotid region Four years' duration in a patient, age 24 Recovery, with cure of the aneurysm Proc South Med Assn (Surg Sect) meeting held at Birmingham, Ala, November 15-18, 1932 South Med Jour , 26, 820-826, 1933
- ⁷⁸ 1932—Subclavian Arteriovenous and Arterial Aneurysms Discussion of Dr J M Mason's paper at the Miami meeting of the South Surg Assn, December 13-15, 1932 Am Jour Surg , 20, 532-539, 1933
- ⁷⁹ 1933—On the Indications and Methods of Surgical Treatment in Dealing with Aneurysms of Special Regions, as these have been evolved in the practice of the author Lecture I, at the Post-graduate Assembly of the Fifth District Medical Society of Southern Texas San Antonio, Texas, January 10, 1933 (No printed transactions)
- ⁸⁰ 1933—A moving picture clinic of the "Methods of Treating Arterial and Arteriovenous Aneurysms in the Practice of the Author " Lecture II, at the Post-graduate Assembly of the Fifth District Medical Society of Southern Texas San Antonio, Texas, January 12, 1933 (No printed transactions)
- ⁸¹ 1933—On the Use of Removable Aluminum Bands (Matas-Allen) in the Surgery of the Great Blood Vessels A preliminary test of the efficiency of the circle of Willis in all operations involving the possible occlusion of the common and internal carotid, and other applications to the surgery of the subclavian, innominate and iliac arteries A Round Table discussion, illustrated with lantern slides Lecture III, Post-graduate Assembly of the Fifth District Medical Society of Southern Texas, San Antonio, Texas, January 13, 1933 (No printed transactions)
- ⁸² 1933—So-called Primary Thrombosis of the Axillary Vein Caused by Strain Report of a case with comments on diagnosis, pathogeny and treatment of this lesion in its medicolegal relations Trans So Surg Assn, December, 1933 Am Jour Surg (n s), 24, 642-655, June, 1934
- ⁸³ 1933—Discussion on Vascular Surgery with Special Reference to the Surgery of the Carotid Tracts The Use of Special Compressors and Aluminum Bands Trans So Surg Assn, Am Jour of Surg , 24, 692-698, December, 1933 (illus)
- ⁸⁴ 1934—(1) Address on the History and Significance of the Violet Hart Award for Outstanding Achievements in Vascular Surgery, and (2) Presentation and Citation of Dr Mont R Reid, first recipient of the "Matas Medal" of the Violet Hart Fund Report of proceedings at Dixon Hall, New Orleans, January 23,

- 1934, in *Times-Picayune*, January 24, 1934, *Am Jour of Surg* (ns), 24, No 1 1-35, April, 1934, and editorial
- ⁸⁵ 1934—Suppurative Pericarditis Discussion following paper by Doctor Bunch on this subject Forty-seventh annual meeting of So Surg Assn, Sea Island, Ga, December 11-13, 1934 *Am Jour of Surg*, 28, 644-647, 1935
- ⁸⁶ 1934—On Coronary Occlusion and Abdominal Emergency Discussion of Drs J M T Finney, Jr, and Chas Mohr's paper on this subject Forty-seventh annual meeting of So Surg Assn, Sea Island, Ga, December 11-13, 1934 *Am Jour of Surg*, 28, 644, 1935
- ⁸⁷ 1934—On Aneurysms of the Temporal Artery Discussion of paper by Doctors Winslow and Edwards on this subject Forty-seventh annual meeting of the So Surg Assn, Sea Island, Ga, December 11-13, 1934 *Trans So Surg Assn*, 47, 506-508 1935, *Am Jour of Surg*, 28, 700-702 1935
- ⁸⁸ 1934—On Scalenus Anticus Syndrome Discussion of paper by Doctors Ochsner, Gage and DeBailey on this subject Forty-seventh annual meeting of the So Surg Assn, Sea Island, Ga, December 11-13 1934 *Trans*, 47, 1935 *Am Jour of Surg*, 28, 694-695, 1935 (In relation to subclavian aneurysms)
- ⁸⁹ 1935—Remarks (chiefly historical) on the Treatment of Peripheral Vascular Diseases by Alternate Positive and Negative Atmospheric Pressure by the Paquet Treatment of Reid and Heilmann Discussion following paper on this subject, by Dr Isidore Cohn in Orleans Parish Medical Society, March 11 1935 *New Orleans M and S Jour*, 88, 79-81, 1935
- ⁹⁰ 1935—On Arteriography Discussion following reading of Dr J Ross Veal's paper on 'Recent Diagnostic and Therapeutic Advances in Peripheral Circulatory Disease' *Trans Louisiana State Med Soc*, New Orleans April 29, 1935 *New Orleans M and S Jour*, 88, 687-689, May, 1936 In this connection see editorial *New Orleans M and S Jour*, 87, 245-247, October 1934 "The Matas Operation for Aneurysm in the Light of Arteriography"
- ⁹¹ 1935—Contribution of Louisiana to the Surgery of the Blood Vessels Address at the Centennial Celebration of the Foundation of the Medical School of Tulane University Hutchinson Memorial, June 12, 1935 (Delayed printing for later publication in the author's *History of Medicine in Louisiana*, in advanced preparation)
- ⁹² 1935—Popliteal Aneurysms and their Surgical Treatment An illustrated lantern slide lecture Tulane Alumni Clinics, October 31 1935 (Publication delayed for additional data)
- ⁹³ 1935—Contribution to the Casuistics of Cirroid Aneurysms of the Scalp and Face With Special Reference to their Surgical Treatment (illus) In the testimonial volume dedicated to Professor Presno, of Havana *Revista de Medicina y Cirujia, Habana* Ano XL, No 11, 869-884, November 30, 1935 (Printed in English)
- ⁹⁴ 1935—On the Treatment of Carotid Cavernous Arteriovenous Aneurysms Discussion following Dr W W Dandy's paper on this subject *Trans Am Surg Assn*, 53, 432-436, 1935 *ANNALS OF SURGERY*, 102, 920-924 1935
- ⁹⁵ 1936—Femoral Aneurysms Their Classification and Surgical Treatment (illus) Lecture, Tulane Clinics, November 12, 1936 (Publication purposely delayed for additional data)
- ⁹⁶ 1936—Discussion on "Aneurysms of the Extracranial Internal Carotid Personal Statistics and Conclusions"—following paper by Drs A M Shipley, N Winslow and W W Walker *Trans South Surg Assn*, 49, 58-59, 1936, *ANNALS OF SURGERY*, 105, 698-699, 1937
- ⁹⁷ 1936—On Continued Intravenous Blood Drip of Marriott and Keknick Discussion following reading of Doctor Silverman's paper on this subject Orleans Parish Med Soc, October 12, 1936 *New Orleans M and S Jour*, 89, 545-548, 1937
- ⁹⁸ 1937—Address on the Pioneers in the Transillumination of the Living Vascular

System for Clinical Purposes With Special Reference to the Achievements of the Portuguese School of Vascular Radiographers

- ⁹⁹ 1937—Preamble to the citation and presentation of the Matas Medal to Professor Reynaldo dos Santos, of Lisbon, the second recipient of the Violet Hart Fund
The two addresses above,^{98 99} are published in the report of proceedings of the "Dos Santos" night Edited by Dr Isidore Cohn, Tulane University Press, 1937
- ¹⁰⁰ 1937—Discussion of Dr Fred H Krock's paper on "A Simplified Apparatus for Pressure-Suction Therapy for Vascular Disease" Trans Surg Section, So Med Assn, So Med Jour, 31, No 3, 294, March, 1938
- ¹⁰¹ 1937—Aneurysms of the Circle of Willis Discussion of Doctor Dandy's "Intracranial 'Clip' Occlusion of the Internal Carotid for Aneurysms of the Circle of Willis," with supplementary remarks Trans So Surg Assn, Birmingham, December 7-9, 1937, ANNALS OF SURGERY, 107, No 5, 660-680, 1938
- ¹⁰² 1939—The Experience of the Charity Hospital of Louisiana, on Aneurysmal Diseases (Dry clinic with lantern slides) Thoughts on the "medical aneurysms" with special reference to the aortic and cerebral aneurysms What is the medical and surgical outlook for the cure of these aneurysms? Clinic by invitation, at the Medical School of Louisiana State University, March 28, 1939 In connection with the visit of the American College of Physicians that date (Unpublished)
- ¹⁰³ 1939—Congenital Arteriovenous Angioma of the Arm, Metastases Eleven Years after Amputation (Type of cavernous angioma histologically benign, clinically malignant) Trans So Surg Assn, Augusta, Ga, December 3-7, 1939 ANNALS OF SURGERY, 111, 1021-1045, June, 1940 (Illus)
- ¹⁰⁴ 1940—Discussion on "Prevention of Ischemic Gangrene Following Operations upon the Major Peripheral Arteries by Chemical Section (alcoholization) of the Cervicodorsal and Lumbar Sympathetics," by Drs Idys Mims Gage and Alton Ochsen Trans Am Surg Assn, 58, 1940, ANNALS OF SURGERY, 112, 957-959, November, 1940
- ¹⁰⁵ 1940—Discussion on "Experimental Studies in the Occlusion of Large Arteries," by Dr Herman E Pearse Trans Am Surg Assn, 58, 1940 ANNALS OF SURGERY, 112, 934-937, November, 1940
- ¹⁰⁶ 1940—Final pictorial report on the case of Corinne Dunson, "Successful Ligation of the Abdominal Aorta for Aneurysm of the Bifurcation," to complete the preliminary report referred to in ref 53 and 61 of this bibliography Discussion and illustrations following papers on the successful abdominal aortic ligations of Doctors Elkin and Bigger Trans Am Surg Assn, 58, 1940, ANNALS OF SURGERY, 112, 907-908, November, 1940
- ¹⁰⁷ 1940—Personal Experiences in Vascular Surgery An historical sketch and statistical summary, covering the period 1888-1940 Trans Am Surg Assn, 58, 1940, ANNALS OF SURGERY, 112, 802-839, November, 1940
- ¹⁰⁸ 1940—Vascular Tumors Piersol and Bartz's Cyclopedia of Medicine, Surgery and the Specialties Vol 15, 798-878, 2nd edition, revised, illustrated and augmented, 1940 Davis and Co, Philadelphia

The foregoing summary has been prepared as an introduction to a series of articles by the author, to appear serially in the ANNALS OF SURGERY These will include the "Surgery of Aneurysm Its Regional Aspects," with the thought of eventually incorporating the essays into a monograph on the subject

JAMES T PILCHER

CLINICAL AND EXPERIMENTAL OBSERVATIONS ON ARTERIOVENOUS FISTULAE*

EMILE HOLMAN, M D

SAN FRANCISCO, CALIF

FROM THE LABORATORY FOR SURGICAL RESEARCH STANFORD UNIVERSITY SCHOOL OF MEDICINE

IN 1923, Lewis and Drury¹ presented observations on arteriovenous fistulae in man and in the experimental animal which were quite limited in scope, in that the clinical fistulae were apparently not operated upon, and the experiments dealt only with the immediate effects of a fistula in an animal which did not survive the experiment. Because of the obvious limitations of such observations, a number of the conclusions which were drawn up have since proved untenable. More specifically, cardiac output was said to be unchanged, whereas numerous observations^{2, 3, 4} indicate that it is markedly increased and even doubled in the presence of a fistula. Fistulae were said not to affect venous pressure, although some of their own observations, and many observations by others, show a very definite increase and sometimes doubling of venous pressure proximal to a fistula, depending on the size of the fistula.

The dilatation of the heart was said to be due to the effect of deficient nutrition incident to a lowering of mean arterial pressures, whereas Green⁵ showed an increased coronary flow due to systolic elevation, and others have demonstrated a degree of cardiac hypertrophy in dilated but properly functioning hearts totally incompatible with a deficient nourishment of cardiac muscle.

Since that time, a number of fistulae in man have been carefully studied before and after elimination of the fistulae, and numerous experimental animals have been observed before and after comparable fistulae were established between the larger vessels and permitted to remain for periods as long as seven years. In a number of instances, observations diametrically opposite to those of Lewis and Drury were made, and they are presented as substantiating the following concepts:

(1) That a fistula introduces a secondary or "fistulous" circuit into the circulatory system.

(2) That the lowered peripheral resistance in this secondary circuit results in a diversion of blood from the primary circuit with its high capillary resistance, the extent of such diversion and the consequent physiologic effects of such diversion depending upon the size of the fistula and its location in the arterial tree.

(3) That the diversion of blood from the normal arterial bed through the fistula into the capacious venous system proximal and distal to the fistula

* Read before the American Surgical Association, St. Louis, Mo., May 1, 2, 3, 1940.

This study was aided by a grant from the Fluid Research Fund of the Rockefeller Foundation.

results in a lowering of blood pressure in the primary circuit, which may be fatal if the fistula is large, or if it lies between the larger vessels

(4) That, following the production of a nonfatal fistula, the general blood pressure is lowered, the diastolic pressure permanently, but the systolic pressure is gradually restored to normal or even above the normal level by the compensatory phenomena of (a) an increased cardiac output through an acceleration of pulse rate in the presence of an increased venous filling, and (b) an increased total blood volume

(5) That venous filling is increased as shown by an increase in venous pressure proximal to a fistula

(6) That in a normally functioning, dilatable heart, this increased venous filling is easily disposed of by accelerated contractions and increased cardiac thrust without a rise in "general" venous pressure

(7) That the part of the circulatory bed common to both the primary and the secondary circuits has an increased volume of blood flowing through it

(8) That an "adjustment" dilatation of this part of the circulatory system occurs commensurate with the increased volume of blood flowing through it, the dilatation involving the artery and vein between the heart and the fistula, and all the chambers of the heart

(9) That, when the fistula is first opened, this adjustment dilatation first involves only the thin-walled easily distensible, capacious venous bed, which, both proximal and distal to the fistula, receives blood under arterial pressure

(10) That the immediate effect of the loss and diversion of blood from the primary arterial bed into the capacious venous bed is a decrease in the size of the heart, followed, in the nonfatal fistula, as the lowered blood pressure incident to this diversion is compensated by an increase in total volume of blood, by a gradual dilatation of the heart and of the artery proximal to the fistula, the final result being a dilatation of the entire circulatory bed through which the short-circuited blood flows

(11) That closure of a fistula results in a reversal of all these changes, primarily as the result of the filling of the primary circuit by the blood formerly flowing through the secondary or fistulous circuit

- (a) An overdilatation of an already dilated heart for 12-24 hours
- (b) A permanent elevation of diastolic pressure due to the elimination of an area of low peripheral resistance
- (c) A transient elevation of systolic and diastolic pressures for several days due to the distention of the arterial bed by the volume of blood increased in the presence of the fistula
- (d) Gradual reduction in the size of the heart and vessels to and from the previous site of fistula due to the reduction in the volume of blood flowing through that part of the circulatory bed common to both the primary and secondary circuits

CLINICAL EXPERIENCES

Case 13 —C H, age 21, entered San Jose Hospital, March 31, 1932, six weeks

* Cases 1 to 12, inclusive, have been previously reported (see references 6 to 11)

after an accidental gunshot wound—the bullet of a .38-caliber pistol having entered the right thigh, laterally, coursing downward to lie under the skin on the inner aspect of the thigh just below Hunter's canal. Little difficulty had been experienced in controlling bleeding, and prompt healing of the wound occurred. About ten days after the injury, the patient first noticed a "puri" on placing his hand on the lower thigh, and in the days that followed, an expansile swelling gradually developed over this area.

Physical Examination—When first seen by me, April 4, 1932, a continuous thrill and bruit were present over this swelling, most intense about six inches above the patella, directly in line with the femoral artery. Pressure over the site of maximum thrill successfully abolished the expansile pulsation in the large swelling and no changes in pulse rate or blood pressure were noted. It was assumed, therefore, that the fistulous opening was small, and the patient was put to bed for complete rest to determine the possibility of spontaneous closure. During the week, definite improvement occurred, the swelling decreased and the thrill and bruit seemed to diminish. No changes in blood pressure or pulse occurred on closure of the fistula by digital pressure, and, accordingly, operation was again deferred. At the end of the next week, the situation was exactly the same as at the preceding examinations, except for one fact. Closure of the fistula produced an appreciable increase in blood pressure from 118/55 to 124/64 and a drop in pulse rate from 88 to 80. This was considered conclusive evidence that a large fistula was present and that it probably would not close spontaneously.

Operation—April 21, 1932. Spinal anesthesia. Because of the large pulsating swelling of the thigh, which was undoubtedly a false sac into which the fistula opened, the operation was performed under a tourniquet applied just below the groin. A long incision paralleling the femoral vessels was made in the midthigh. After displacing the sartorius muscle medially, a large false sac was entered and about a quart of organized and clotted blood was evacuated. The femoral artery was exposed and just above Hunter's canal, a rent 1.5 cm long was found opening into the false sac. A similar rent was found in the companion vein, which also opened into the false sac but the vein was in no way adherent to the artery. The artery and vein were ligated above and below the rents, and the vessels divided between the ligatures.

On removing the tourniquet, definite pulsation was noted in the stump of the ligated distal artery, indicating an adequate collateral circulation. At the end of the operation, the foot was warm and pink and a good pulse could be felt in the posterior tibial artery. An uneventful recovery followed.

Case 14—W. B., age 38, entered Lane Hospital, March 7, 1933, three months following a gunshot wound of the right thigh. The bullet from a .22-caliber rifle entered the lateral thigh six inches above the knee, shattered the shaft of the femur, and lodged under the skin on the medial surface. He was taken to a hospital where the leg was placed in a Thomas splint. No nerve or vessel injury was suspected at that time. Three weeks later after sneezing, there was a sudden onset of throbbing pain in the lower thigh, which then began to swell to such proportions that the skin became tense and shiny. The pain was intense, a fever developed, but after a week both subsided. He was told that he had an arteriovenous fistula, but that operation would have to be deferred to await the development of collateral circulation. He left the hospital at his own request. Two weeks after leaving the hospital, a throbbing pain and fever again appeared, and he entered Lane Hospital for the surgical treatment of the fistula.

Physical Examination—The heart was not enlarged, the sounds were normal, blood pressure, 100/66, pulse rate 84, the red cells 3,760,000, hemoglobin 61 per cent (Sahli), leukocytes 7,400. The right thigh was markedly swollen in the lower half of the medial and anteromedial surfaces. At the level of greatest swelling the circumference of the right leg was 50.4 cm, left leg 37 cm. There was no visible pulsation, but a palpable one, and directly over the peak of the swelling there were a slight thrill and a continuous bruit, intensified in systole. The dorsalis pedis and posterior tibial pulses were absent on the right, normal on the left. There were no objective sensory changes although the leg felt numb. The femoral artery on the right felt stronger than on the left, but com-

pression of the artery failed to produce any consistent alterations in the pulse or blood pressure. The continuous thrill and bruit, however, made the diagnosis of arteriovenous fistula a certainty, complicated by a large false aneurysmal sac.

Operation—March 10, 1933. A tourniquet was applied just below the groin, and a long incision made from the medial aspect of the knee to a point halfway up the thigh, paralleling the course of the vessels. The muscles were separated in the direction of their fibers, and a large false sac was entered, evacuating a great amount of blood clot. At the bottom of the sac were the femoral vessels, each one with a large defect in its wall, approximately 2.5 cm long each rent opening separately into the false sac. Only a small segment of the wall of each vessel remained intact (Fig. 1).

The blood from the artery poured first into the false sac, and was then forced through the opening in the vein. The variable amount of blood flowing through the sac accounted for the variable effects of the fistula noted before operation. It seems probable that when the pressure in the sac became almost arterial, it tended to collapse the vein and

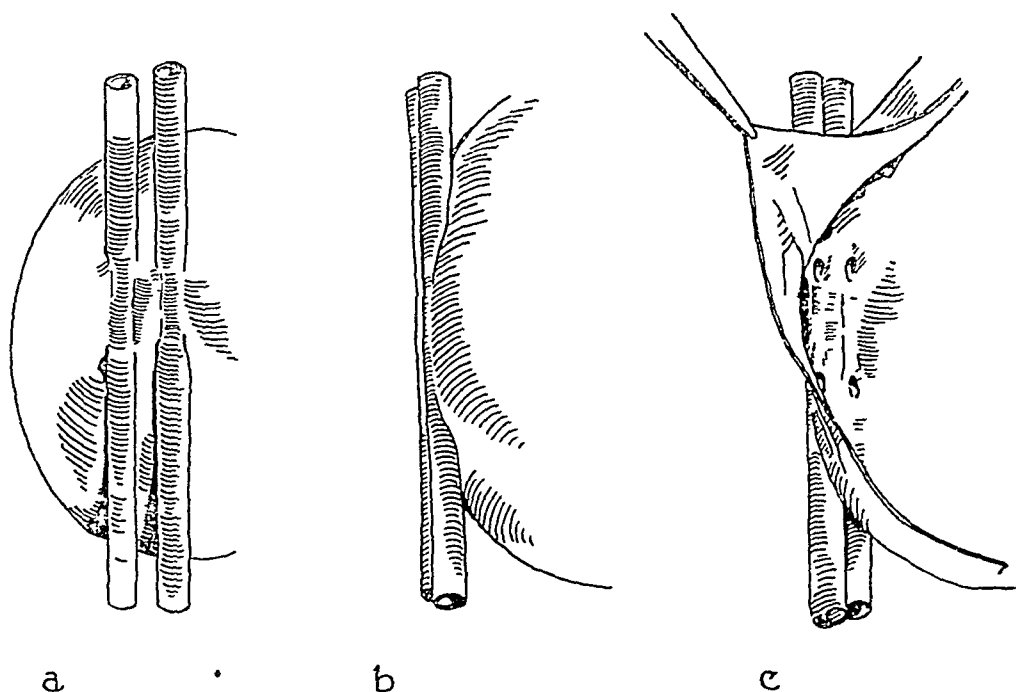


FIG. 1.—Case 14. Diagrammatic presentation of an unusual type of arteriovenous fistula of popliteal vessels. Proximal artery and vein both open into a large false sac with separate openings into distal artery and vein. Quadruple ligation and excision performed. Restoration of vessels impossible. No impairment of circulation.

its opening, the flow of blood would cease temporarily, the continuous murmur would cease, and other attributes of a fistula would disappear. It was obviously impossible to restore the continuity of the artery, and, accordingly, a quadruple ligation was performed, the artery and vein divided between the ligatures, thus permitting their retraction. The tourniquet was removed and all bleeding points were controlled. A good pulsation was present in the stump of the distal artery, indicating an adequate collateral circulation. At the completion of the operation the color of the foot was excellent, although the posterior tibia and dorsalis pedis pulses were absent. An uneventful recovery followed. On dismissal the general blood pressure was 104/72.

Case 15—C. S., age 23, entered Lane Hospital, October 17, 1933, complaining, mainly, of recurring ulcers of the left leg since a gunshot wound of the left thigh four years previously. The shot entered the left thigh just below Poupart's ligament, apparently grazed the femur, a fragment of the bullet being recovered from underneath the skin posteriorly. The initial marked bleeding was surprisingly easily controlled. Immediately after the injury, the distal part of the extremity increased greatly in size, within a short time prominent varicosities appeared over the entire left leg, and within a year, the first ulcer



FIG 2—Case 15 Femoral fistula of four years' duration. Note marked dilatation of proximal artery and great distention of all veins in the presence of the fistula and their complete disappearance after operation.



FIG 3—Case 15 Cardiac dilatation of marked degree accompanying a femoral fistula of four years duration. Blood pressure markedly affected by closure of fistula. Total blood volume decreased 1,000 cc and heart size markedly decreased within 30 days following elimination of fistula.

ARTERIOVENOUS FISTULAE

appeared on the lower leg followed by alternate healing and recurrence. A rumbling thrill at the site of injury was noted a few weeks after the accident and had been present ever since. There were no other complaints except a moderate thumping of his heart and beating in his ears, more pronounced after exercise, although it had not interfered with his work.

Physical Examination—The left leg was markedly swollen in the dependent position (Fig 2), visibly less in the horizontal position, and almost not at all with the leg elevated 45°. In this elevated position, definite visible pulsation was observed in the superficial veins of the thigh and leg down to the level of the ulcer on the anterior surface of the lower leg. There was marked pigmented discoloration of the skin around this ulcer and the leg, as a whole, was cyanotic as compared to the normal right leg. Just below Poupart's ligament was an area of visible pulsation about 3 cm in diameter, into which ran a greatly dilated, palpable femoral artery. A very pronounced thrill and bruit were present over the area of visible pulsation, the bruit extending well up into the abdomen. The heart was greatly enlarged, the apex beat being in the sixth interspace at the anterior axillary line (Fig 3 a). There was a soft systolic murmur at the apex. The radial pulse had a collapsing character, comparable with that of an aortic insufficiency. The posterior tibial and dorsalis pedis pulses were absent. On occluding the fistula by digital compression over the common femoral artery and vein, the whole lower leg became suffused with blood, and the varicosities became greatly distended.

TABLE I—Case 15

BEFORE OPERATION

DATE	R B C	W B C	Hb	Blood Pressure		Pulse		Blood Volume	O ₂ Content Venous Blood	
				Fistula Open	Fistula Closed	Open	Closed		L Leg	R Leg
10-17-33	6 3	7800	95							
10-18-33				140-55	160-100	72	56			
10-19-33	6 0		95	144-56	150-90		64	7200	18.6%	15.0%
10-20-33	5 9			148-54	170-100	84	48			
10-23-33			96		158-90					
10-24-33	6 1									
10-27-33	5 5		96							
10-28-33				124-60		88				

OPERATION FOR ELIMINATION OF LEFT FEMORAL FISTULA

10-28-33 3 PM	6 3		118	144-94		72				
6 PM				156-104		80				
9 PM	6 5		117	158-106		78				
10-29-33	6 2		108	152-94		64				
10-30-33	6 2		107	164-92		74				
10-31-33	6 1		107	145-82		78				
11-1-33	5 4		104	138-72		76				
11-3-33	5 8		107	148-82		62				
11-4-33	5 3		99	128-72		60				
11-6-33	5 5		98	126-74		60				
11-8-33	5 2		96	124-70		78				
11-10-33	5 2		96	118-70		80				
11-13-33	4 9		90	116-70		64				
11-15-33	5 2		91	130-80		64				
11-27-33	5 0		95	118-76		60		6200		
8-29-35	4 8		84	120-75		76				

Skin temperatures as determined by a thermocouple were as follows

	Right	Left
Forearm	32.0°C	32.0°C
Midcalf	31.0°C	33.5°C
Sole	27.5°C	28.0°C

The increased surface temperature of the left lower leg was consistent with the arterial pulsation in the superficial veins, indicating the presence of arterial blood close to the surface.

Specially taken roentgenograms of the left femur showed it to be 2 Mm longer than the right.

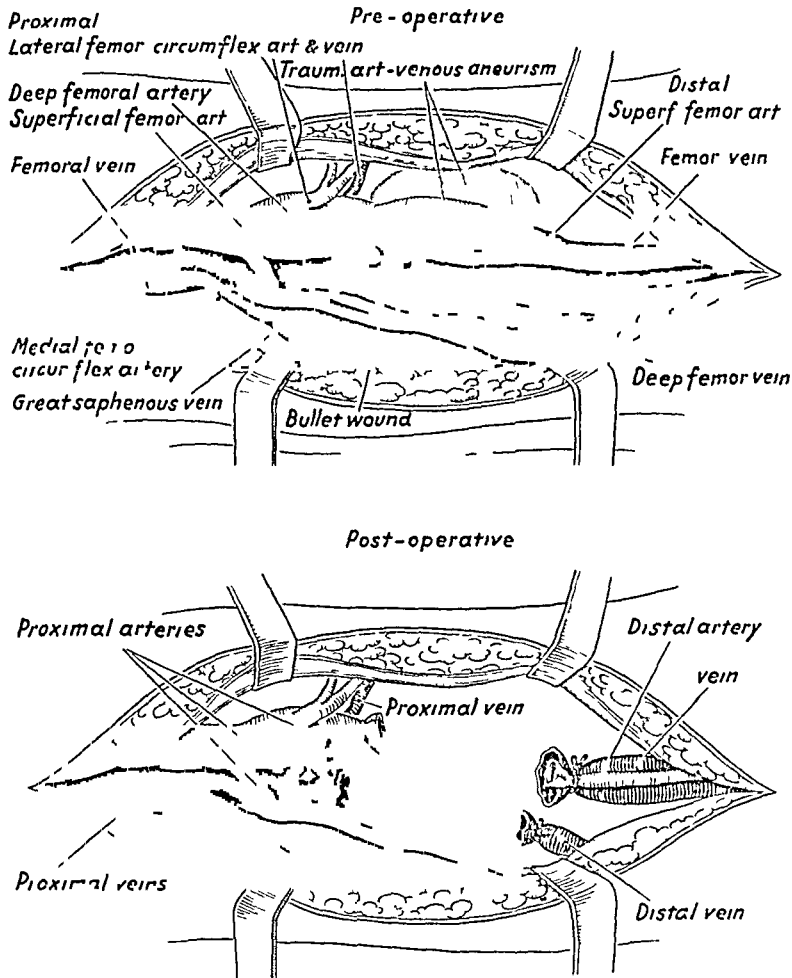


FIG. 4.—Case 15. Conditions found at operation for elimination of femoral fistula of four years duration. Ligation of both deep femoral and superficial femoral arteries was uncomplicated by impairment of nutrition.

During fluoroscopic examination, the heart was seen to increase 5 Mm. in diameter on closing the fistula. Special studies are recorded in Table I.

Operation—October 28, 1933. Elimination of the fistula was performed without a tourniquet. A 20 cm.-long incision was made over the course of the femoral vessels. The large common femoral artery and vein were first exposed, isolated and surrounded with tapes which, however, were not tied. The enormously enlarged saphenous vein was displaced medially. The aneurysmal sac, about 3 cm. in diameter, was partially isolated, but a large extension of the sac down to the femur and into the soft tissues of the posterior

ARTERIOVENOUS FISTULAE

thigh was not isolated. It was found that both the superficial and deep femoral arteries entered directly into the aneurysmal sac, that the blood left the aneurysmal sac by passing into a small, almost obliterated superficial femoral artery, whereas the greater volume of the blood passed directly into a very large superficial femoral vein. It was apparent that the pulsation in the popliteal space which was attributed before operation to a large popliteal artery was in fact a pulsating popliteal vein. The vessels entering and leaving the sac were doubly ligated and the sac excised, except for the portion extending posteriorly (Fig 4). The arteries ligated in this maneuver were the superficial femoral artery just beyond the emergence of the deep femoral artery but proximal to the aneurysm, the superficial femoral artery beyond the aneurysmal sac, the deep femoral artery just distal to the lateral circumflex branch, but proximal to its entrance into the aneurysmal sac. No deep femoral artery was identifiable beyond the aneurysmal sac. The saphenous vein was spared. The superficial femoral vein was ligated proximally

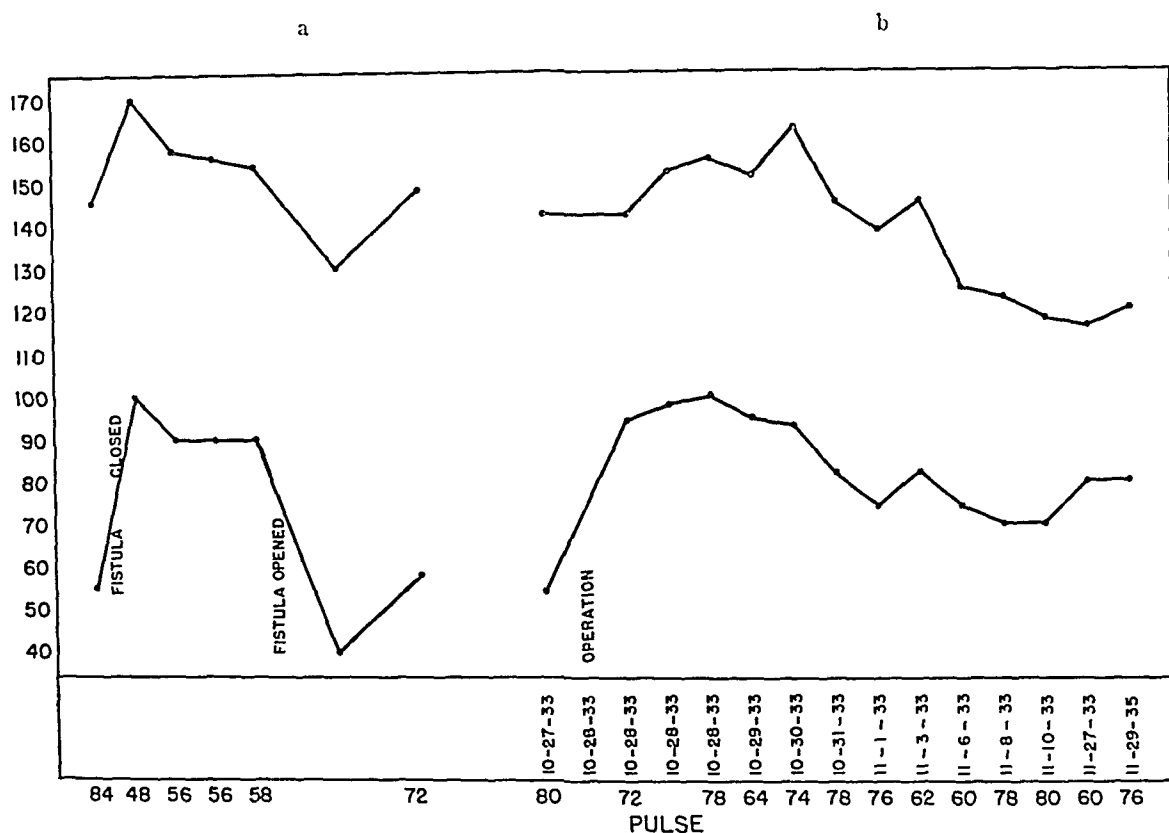


CHART 1—Case 15 Showing the variations in blood pressure incident to closure of a femoral fistula of four years' duration (a) By digital pressure, (b) by operative elimination

The blood volume decreased from 7,200 cc to 6,200 cc following operative removal of the fistula and distally to the aneurysmal sac, as were also several larger venous tributaries in the region of the deep femoral artery. The partially excised aneurysmal sac contained about two ounces of blood. The walls of that portion of the sac still remaining in the tissues were approximated with interrupted sutures. Although no pedal pulses were palpable, the foot was warm and pink at the end of the operation. At the beginning of the operation the blood pressure was 124/60, pulse rate 88. At the end of the five-hour operation it was 140/90, pulse rate 72. No fluids were administered either subcutaneously or intravenously during the operation.

The later behavior of the pulse and blood pressure are recorded in Chart 1. Blood studies (Table I) revealed a concentration of hemoglobin from 96 to 118 per cent (Sahli), and a concentration of red cells from 5.5 to 6.5 million in the first 24 hours after the operation.

In the course of the operation, a number of fragments of the original bullet were recovered, a few lying partially imbedded in the wall of the posterior extension of the aneurysmal sac. On the fourteenth day following the operation, the wound was reopened

and a large abscess evacuated, the pus coming from the blind aneurysmal sac in the posterior thigh. The wound was debrided and an uneventful healing occurred. The heart gradually decreased in size, and four weeks after operation the total blood volume had dropped from 7,200 cc to 6,200 cc. The pounding in his heart and head was no longer present after the operation. The ulcer of the lower leg rapidly epithelized, and was healed on discharge. Two years later, he returned for the injection of some prominent varicose veins of the left leg just above two small ulcers in the same area of previous ulceration. In other respects he was perfectly well.

Case 16—S. H., age 22, entered Lane Hospital, March 8, 1937, because of an arteriovenous fistula of the left thigh, from which he had experienced no symptoms whatever, but which had been the cause for the rejection of a recent application for life insurance. He was told by his physician that unless the fistula were eliminated he would develop heart trouble.

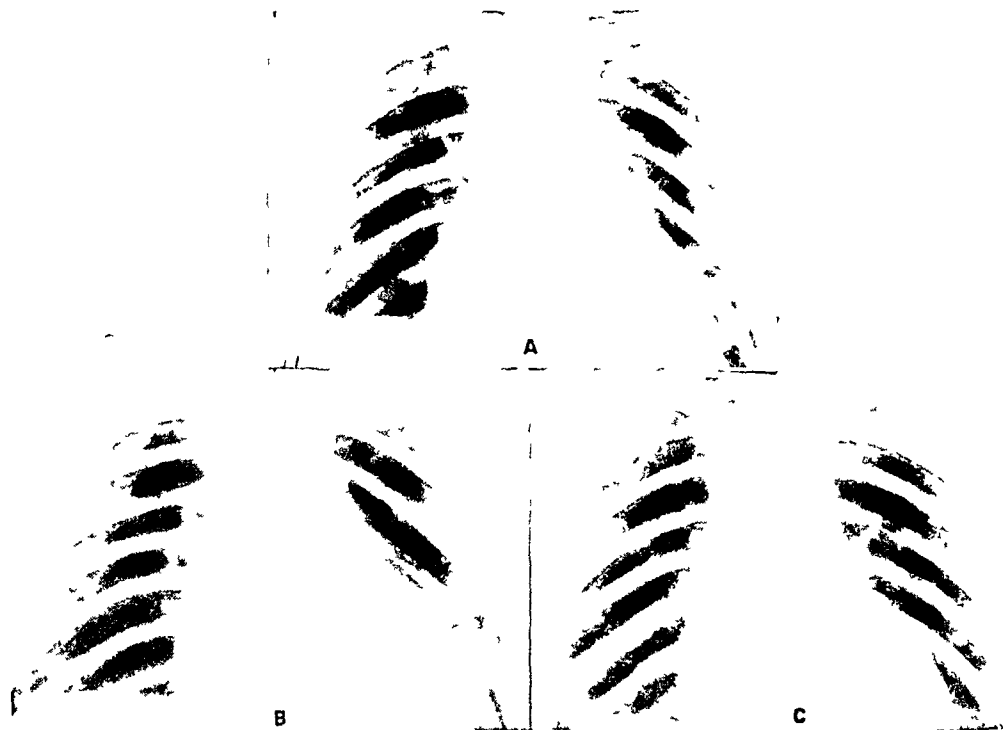


FIG 5—Case 16 (A) Cardiac dilatation in the presence of a femoral fistula of five years' duration, is (B) definitely increased 24 hours after the closure of the fistula, but (C) markedly decreased within 48 hours.

Five years previously, while on a camping trip, he had been shot accidentally through the left thigh by a 22-caliber pistol at a distance of about ten feet. The considerable bleeding which occurred was controlled immediately with a tourniquet, and there was no recurrence of bleeding. At the hospital, four hours later, a local debridement was performed, and he was discharged two weeks later with the wound healed, but with a "purr" in his thigh, which he himself discovered after his discharge, but which he did not call to his doctor's attention. There had been no cardiac symptoms, except an occasional light-headedness and a pounding in his heart noted only when lying down. He was a store clerk and had experienced no shortness of breath. His doctor noted a cardiac murmur for the first time about nine months before admission.

Physical Examination—Temperature of 37.2°C , pulse rate 76, respirations 18. There was almost no swelling of the affected leg, even the superficial veins were not prominent. In the midthigh were a marked palpable thrill and audible murmur continuous throughout the cardiac cycle with great systolic accentuation. These were

ARTERIOVENOUS FISTULAE

maximum at a point midway between the pubic spine and internal condyle of the femur, but they could be felt and heard both distally and proximally to it, even over the lower abdomen

There was marked increase in the precordial activity, and as the patient lay on his back one could see vigorous pulsation of the abdominal aorta, extending into the left inguinal region, continuing down the left femoral artery but ending abruptly in its midpoint at the presumed site of the fistula. On palpation, the left femoral artery appeared to have a diameter of approximately 9-10 Mm, whereas the right femoral artery felt about 5-6 Mm in width. The popliteal, posterior tibial, and dorsalis pedis arteries could be easily felt on both sides. When the fistula was digitally compressed sufficiently to obliterate the thrill, the posterior tibial pulse below it was stronger than before, indicating a more than adequate collateral circulation. The heart was enlarged to percussion, measuring 3.5 cm to the right and 10.8 cm to the left of the midline (Fig 5). A systolic

TABLE II—Case 16

BEFORE OPERATION

DATE	R B C	W B C	Hb	Vital Capacity	Blood Volume	Venous Pressure Right Arm		Water Balance		Icterus Index	Pulse	Blood Pressure
						Fistula Open	Fistula Closed	Intake	Output Urine			
3-8-37	4.6	8600	86							88		
				4250		120	100	2500	1200		76	128-52
3-9-37				4300	5040	105	91	2500	800			
3-10-37						114		2500	1000			
3-11-37	4.8		99								80	138-58
3-12-37	4.5		100					2500	700			

OPERATION 3-13-37

3-13-37	5								400			
2 hrs PO	5.25		103					2500	2700		76	190-80
3-14-37	5.2		101									
	5.4		103								63	176-104
	5.4		104									
3-15-37	5.5		105					2500	1000	6.1	80	172-105
3-16-37	5.4		104					2500	900	6.3	74	176-100
3-17-37	4.9		98					2500	2000	4.4	76	140-70
3-18-37	5.0		100					2500	1950	5.8	72	130-90
3-19-37	4.8		98		4200			2500	650		84	142-88
3-21-37				4500								

murmur could be heard over the entire precordium, greatest at the apex but heard also over both the aortic and pulmonic areas. There was visible distention of the neck veins. The liver dulness was not increased, extending from the upper border of the sixth rib to a finger's breadth below the costal margin.

Studies of the effect upon blood pressure and pulse of closing and opening the fistula are recorded in Chart 2. On closing the fistula by digital compression, the blood pressure rose for a few seconds to 156/90, dropping to a level of 142/80 as long as the fistula was closed. Opening the fistula caused a precipitate drop to 118/48, recovering promptly to 138/56. The pulse rate was affected promptly by the closure of the fistula, dropping from 80 to 66 and 72.

The electrocardiogram was normal in all leads and was not altered by closure of the fistula, except for the drop in pulse rate.

Careful studies of the fundi revealed pulsating arteries and veins and arterioles in the region of a macula of normal size. When the fistula was closed, however, the arteries seemed to engorge and stop pulsating, the veins dilated and pulsated, and the arterioles of the macular region dilated and encroached more closely upon the macula.

Roentgenographic studies of the two femora demonstrated the left femur to be 1 cm longer than the right. Inasmuch as the patient contracted the fistula at the age of 17, when the epiphyses were still ununited, we may ascribe this increased lengthening to the increased vascularity of the left thigh incident to the extensive collateral circulation, which occurs so characteristically in the presence of a fistula.

Fluoroscopically, "the heart is seen to be beating vigorously and at a rather rapid rate. When the fistula is compressed, the pulse rate slows, and the diameter increases 0.5 cm. As the compression of the fistula is continued the pulse rate is slightly accelerated, and the heart becomes even smaller than before closure of the fistula by 0.5 cm. On releasing the compression, the heart returns to its first state in about 30 seconds." These changes confirm previous observations that cardiac size varies with redistribution of the blood volume depending upon conditions at the fistula. The immediate effect of closing the fistula is to back up the previously short-circuited blood in the central arterial bed, particularly the heart, which temporarily dilates. There is a rise in arterial pressure which is promptly compensated by a peripheral dilatation (as seen in the retinal vessels). This filling of the peripheral bed by the blood formerly short-circuited through the fistula removes some of the blood volume in the central circulatory bed, and the heart becomes smaller than it is with the fistula open.

Operation—March 13, 1937. The fistula was exposed by a long incision paralleling the femoral vessels in the mid thigh. A tourniquet was not employed, as full and pulsating vessels are more easily identified and isolated than are collapsed ones. The proximal artery was freed first and a tape applied so as to be able to close it in case of trouble with bleeding. When the vessels and fistula were finally isolated the following measurements were obtained:

Proximal artery	1.0 cm diameter
Proximal vein	2.0 cm diameter
Distal artery	0.7 cm diameter
Distal vein	1.2 cm diameter

Quadruple ligation was performed and the fistulous area excised. By careful measurements the inside diameter of the fistula itself was computed as having had a diameter, in life, of 0.8 cm. The blood pressure at the beginning of the operation was 142/74, pulse rate 84. At the end of the two-hour operation it was 170/90, pulse rate 80. At the moment of ligation of the artery the blood pressure rose temporarily to 190/90, pulse rate 74.

Following operation significant changes occurred in the size of the cardiac silhouette (Fig. 5) in blood pressure (Chart 2), in pulse, and in the blood elements themselves, all changes being dependent upon the increase in total blood volume that occurred in the presence of the fistula, and that required several days for its readjustment to normal. Twenty-four hours after the elimination of this patient's fistula the transverse diameter of the heart had increased from a preoperative measurement of 19.5 cm to 21 cm. Forty-eight hours after the operation the transverse diameter had decreased to 17.5 cm. The temporary postoperative increase in the size of the heart is explained on the basis of a redistribution of the total blood volume, and is the direct opposite of what occurs when the experimental fistula is first opened. Blood which formerly flowed freely through the fistula into a capacious venous system temporarily fills the arterial system, resulting in a temporarily increased general pressure and a temporary overdilatation of the left cardiac chambers, possibly even extending back through the pulmonary vessels to distend the right cardiac chambers as well. Evidence of this is available from a study of roentgenograms made with the fistula open and with it closed. The roentgenologist's report was as follows: "Films were taken with ordinary exposure to show the normal lung

ARTERIOVENOUS FISTULAE

markings The first film was taken without compression of the fistula and the second film was taken five seconds after the fistula had been shut off When the two films were compared, we can see that the peribronchial markings are more prominent in the film taken after the fistula had been closed off The heart measures about 5 Mm more in transverse diameter in the film taken after closure of the fistula"

Following elimination of the fistula by operation the total blood volume decreases the pressure slowly falls, and the heart decreases in size The decrease in blood volume is effected in the first few days by elimination of the plasma resulting in a concentration of the cellular elements and in hemoglobin As noted in the chart, the urinary output

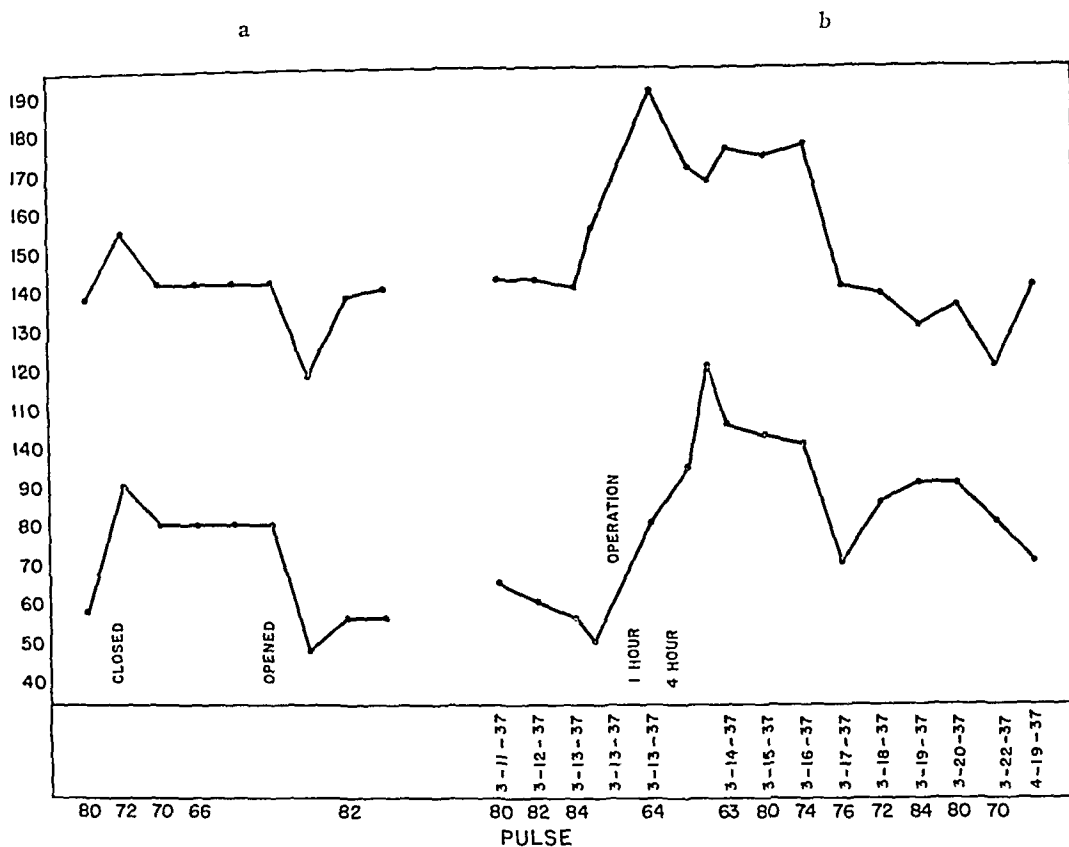


CHART 2—Case 16 Variations in blood pressure incident to closure of a superficial femoral fistula of five years' duration (a) by digital pressure, (b) by operation

The blood volume decreased from 5,040 cc to 4,200 cc following elimination of the fistula

greatly exceeded the intake of fluid during the first two days following the operation, suggesting a readjustment in total blood volume by the elimination of plasma The red cells increased immediately after operation from 45 million per cc to 54, dropping in five days to 48 million The hemoglobin increased from 100 before operation to 105, dropping within five days to 98 The blood pressure and pulse rate behaved as noted in Chart 2 Immediately after operation, the blood which formerly leaked into the capacious venous system of the shorter circuit now filled the arterial system, as shown by an increased distention of the retinal arterioles This overdistention of the arterial system resulted in a postoperative increase in blood pressure in the first few days as high as 190/80 and 172/105, as compared to 138/58 before operation The overdistention of the aorta and cerebral vessels produced a vagal inhibitory effect upon the heart, causing a drop in pulse rate from 80 to 76 and 63 After six days, the blood pressure was 142/88 and pulse rate 84, the diastolic pressure being permanently elevated by the elimination of the lowered peripheral resistance due to the fistula The total blood volume dropped from 5,000 cc before operation to 4,200 cc after operation

Case 17—J H, age 38, entered Lane Hospital, April 3, 1939, on crutches, because of an injury to his left thigh one month previously On March 4, 1939, while cutting linoleum with a knife, the blade accidentally entered the left midthigh to a depth of two

inches. On withdrawing the blade, blood spurted violently (about two yards) with each heart beat. Despite attempts at controlling the bleeding, he promptly fainted, apparently from loss of blood. He was taken to a local hospital where the wound was dressed and found to be filled with clot. About two hours after injury, the wound again broke open, with excessive bleeding, from which he again fainted. He left the hospital after two days, and uneventful healing occurred. The thigh became quite swollen, with black and blue discoloration, which gradually disappeared. He had not attempted weight-bearing because of pain on extension of the leg. A marked dyspnea, which was present for a few days after injury, had disappeared. About six days after the injury he noted a "buzzing" over the wound, which had persisted.

Physical Examination—The heart was normal to percussion, but a loud blowing systolic murmur was heard at the apex. There was no gross difference in the two legs. On the midmedial aspect of the left thigh was a 2 cm scar. Palpation over this area revealed a striking thrill and a small firm mass. On auscultation, a loud, continuous murmur could be heard, intensified in systole, and audible up and down the thigh along the course of the vessels. General blood pressure with the fistula open was 118/72, pulse rate 64. On compressing the femoral artery above the fistula, the blood pressure rose to 134/100, pulse rate 60. The left femoral artery was not demonstrably larger than the right. A good posterior tibial pulse could be felt on the left as well as on the right. The operation for the repair of the fistula was undertaken after only a month had elapsed since the injury because (1) healing had produced a painful thigh on motion, and (2) the changes in blood pressure and pulse rate on closing the fistula indicated a large fistula which, undoubtedly, would eventually have affected the heart, and would, most certainly, not have closed spontaneously.

Operation—April 8, 1939. A tourniquet was not applied at the beginning of the operation. Under avertin and nitrous oxide anesthesia, Hunter's canal was exposed through a long, 15-cm incision along the course of the vessels. The artery and vein were first isolated above the site of the fistula. An aneurysmal sac, 4 cm in diameter, was identified, projecting from the vein, in which swirling arterial blood could be seen. The artery and vein distal to the sacculization were identified and isolated. On closing the artery proximal to the fistula with a clamp, pulsation was still present in the artery beyond the fistula (Henle-Coenen test), indicating an adequate collateral circulation. Despite this evidence, it was decided to ligate and excise the vein proximal and distal to the fistula in order to avoid the dangers of embolism of air or clot and to restore the artery. The vein was ligated above and below the fistulous opening and the intervening segment excised, together with a portion of the aneurysmal sac. The rent in the artery measured 1.2 cm in length and was closed with fine, interrupted, oiled silk sutures, the line of suture being reinforced by suturing the distal stump of the vein so as to lie snugly over it. An excellent dorsalis pedis and posterior tibial pulse could be felt at the end of the operation. The blood pressure at the beginning of the operation was 104/70, pulse rate 80, and at the end of the three-hour operation it was 150/90, pulse rate 64. An uneventful recovery followed. No fluids were administered either subcutaneously or intravenously during the operation.

Case 18—A W, age 36, on September 19, 1932, accidentally sustained a gunshot wound, the bullet from a 32-40 deer rifle entering the right upper chest and emerging through the muscles at the base of the right neck. The furious bleeding which ensued was with difficulty controlled by digital pressure and dressings. No operation was performed, but the patient was apparently unconscious for about two hours. On the following morning, his local doctor noted a constant murmur in the right upper chest. The hand and arm felt numb for about a week, followed by a slow recovery except for a persisting numbness in the index finger. He returned to work exactly a month after the accident and continued his work as a clerk until 1937.

In April, 1933, he consulted a surgeon at the request of his local doctor. His com-

ARTERIOVENOUS FISTULAE

plaints at this time were paresthesia of the upper arm brought on by muscular movements of the arm, particularly abduction, numbness of the index finger, variable soreness of the right shoulder, and a booming sound in his right ear. Examination at this time showed a man apparently in robust health. His heart was of normal size (Fig 6 a), there were no murmurs. Blood pressure was 140/80 in both arms, pulse 90. The scar of wound of entrance lay in the third interspace just to the right of the sternum, and

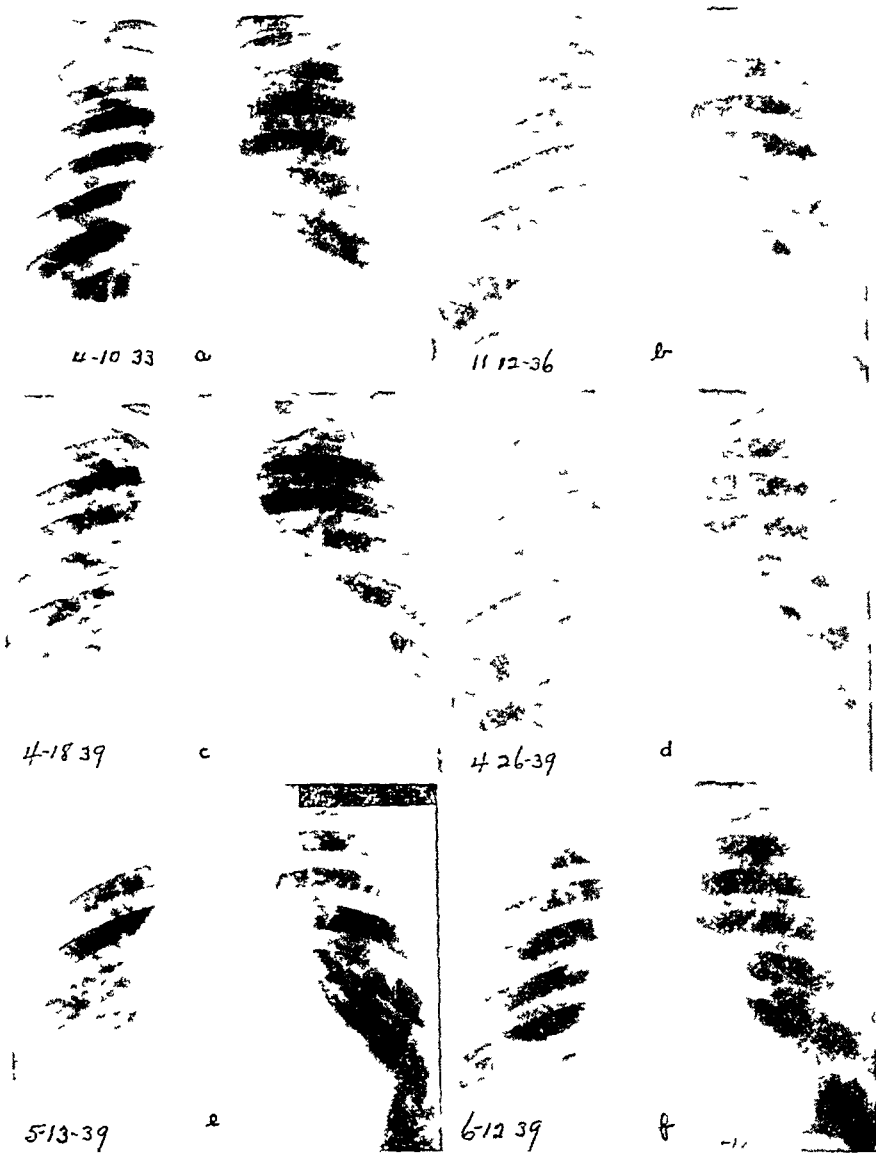


FIG 6—Case 18. Cardiac silhouettes in the presence of an arteriovenous fistula. (a) Six months after establishment of a right subclavian jugular fistula. (b) Three and one half years later—patient only slightly incapacitated. (c) Six and one half years after injury when complete cardiac decompensation was present—generalized edema, ascites and hydrothorax. (d) Great improvement after one week's complete rest. (e) Three days after operation. (f) Thirty three days after operation, all evidence of decompensation absent. The great vessels at the root of the heart are dilated, as well as the heart.

the scar of wound of exit lay on the ridge made by the trapezius muscle. There was no evidence of injury to the clavicle. In the right supraclavicular space was a slight swelling, and in this region one could hear a continuous bruit intensified in systole, which was modified but not obliterated by pressure just above the inner end of the right clavicle. Very deep and somewhat painful pressure at this point caused a fall in pulse rate from 84 to 76 per minute, and a very slight increase in blood pressure, from 138 to 144 systolic. There was slight atrophy of the muscles of the right forearm, but muscular movements and sensation were normal. In view of the apparent inaccessibility of the

lesion and because of its presumably innocuous character, the consulting surgeon advised against operation with the admonition to return for periodic observation. He was not seen again by this surgeon until September, 1936, when he returned complaining of increasing weakness, increasing shortness of breath, loss of weight, great nervousness due to the noises and "pounding" in his right chest, neck, and head, which were always worse in the night. Slight exertion produced great exhaustion, as did a heavy meal.

Physical Examination—The patient was still in apparently good health, but his heart was larger than before (Fig 6 b), and a faint systolic murmur could be made out

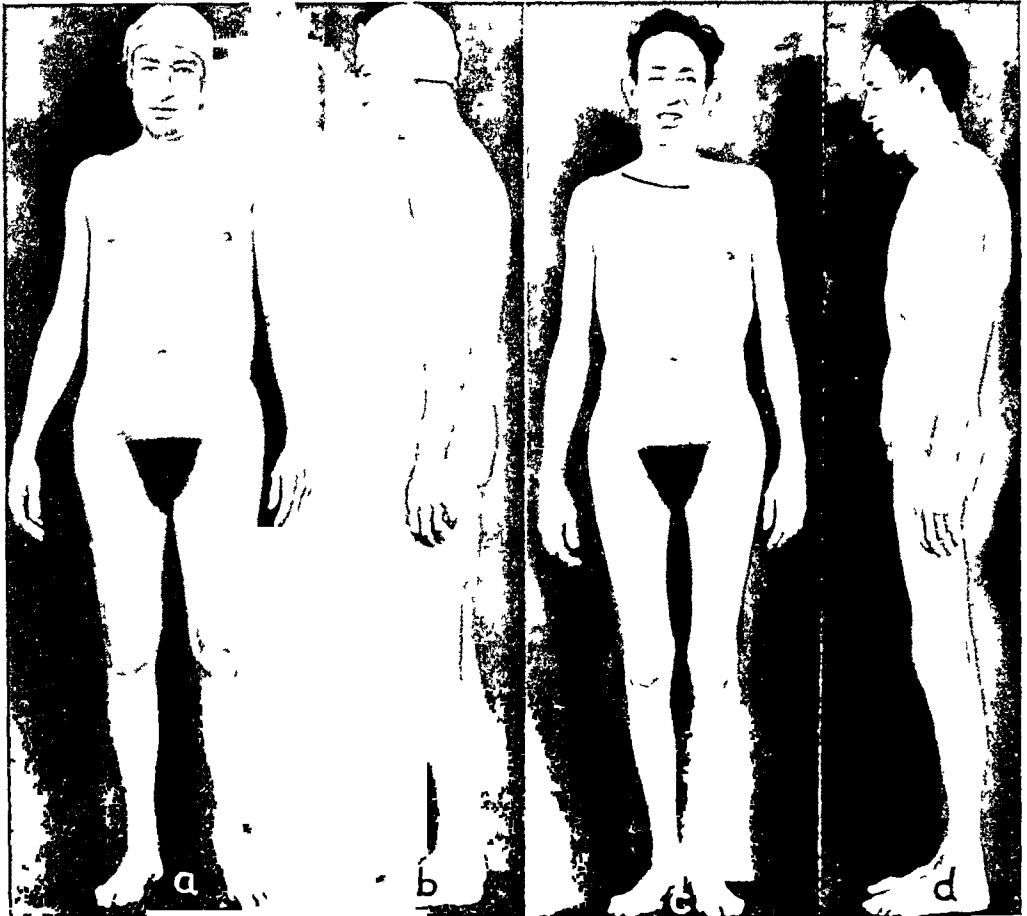


FIG 7—Case 18 (a b) On admission, this patient showed complete cardiac decompensation including severe brawny peripheral edema, ascites and hydrothorax due to right subclavian jugular fistula of six and one half years duration. (c d) Complete recovery with loss of ascites and edema 12 days after elimination of fistula. Horner's syndrome, which was quite noticeable at this time later practically disappeared. Line marks the incision.

at the apex. The other normal cardiac sounds were completely submerged by the tremendous roar emanating from the fistula. Deep pressure just above the inner end of the clavicle again modified the bruit but did not obliterate it. Blood pressure readings in the left arm were 125/55, right arm 122/55, pulse 90. On partially closing the fistula by painful digital pressure, the pulse dropped from 90 to 82 and the general blood pressure rose from 125/55 to 142/80. Despite the obvious increasing deleterious effects of the fistula, he again left the hospital without operation—the surgeon being impressed by the apparent impossibility of operating successfully upon a fistula lying presumably between the innominate vessels. In May, 1937, a right inguinal hernia was repaired under local anesthesia.

In April, 1939, he was referred to the Stanford Surgical Clinic. His story, since 1936, had been one of increasing breathlessness and easy fatigability, increasing dyspnea and palpitations on exertion, inability to work for two years, nocturnal dyspnea for two years, transient edema of the feet for two years, which finally became permanent four months ago when the edema extended upward to involve both thighs and, in the past two months, the abdomen as well. Dizzy spells and a persistent cough had also accompanied the increasing dyspnea. He had noted also a progressive weakness of the right arm and hand, which became quite purple and cold when all other extremities were pink and warm. When first seen on this admission he showed all the evidences of an advanced cardiac decompensation. He was markedly dyspneic, even while lying in bed. His face was cyanotic, the tissues everywhere slightly edematous, his lower extremities hard and indurated with edema, his abdomen prominent due to an advanced ascites (Fig 7). There was marked venous distention of the cervical veins on the right, with visible pulsation in one small venous branch, and a vigorously pulsating carotid artery. A continuous thrill and bruit could be easily made out over the right upper chest and neck, most prominent just over the medial end of the clavicle. The heart was greatly enlarged with evidence of râles and increased dullness at both pleural bases. The urine showed no abnormalities. The plasma protein was 5.4 mg, the albumin 3.3 mg per 100 cc. The following examinations were of more than usual interest (Table III).

TABLE III—Case 18
BEFORE OPERATION

Date	Weight Kg	WBC	RBC	Hb	Pulse	Blood Pressure		Vital Capacity cc	Circulation Time in seconds		Venous Pressure cm of water		Icterus Index	Blood Volume cc
						Right arm	Left arm		Right arm	Left arm	Right arm	Left arm		
4-8-33	77.2				90	140-80	140-80							
11-13-36	66				90	120-55	125-55							
4-18-39	79	10,260	5.25	105	120	142-86	130-78	1900	30	25	18	20.5	14	8080
4-24-39	62.5	7,200	5.55	112			118-64	2900	28	30	15	11		
4-27-39								3100					8	7700
5-2-39		10,400	5.1	92	82	118-60	122-64	3200	27	27	13.5	10.5		
5-9-39	62.2					116-58	116-58							7560

ELIMINATION OF FISTULA 5-10-39

5-10-39			5.21 5.28	98 100	80		114-74							
5-11-39			4.8 4.97	91 97	80		140-60							
5-12-39					80		134-70							
5-13-39					84		132-80							
5-15-39					64		130-80						12	
5-16-39					78		134-84							
5-17-39					80		140-90							
5-18-39	58								30	17	20	8		6380
6-7-39	63				80	78-7	124-66	3300						5375
6-12-39									27	15	21	10		
6-19-39					88		104-68						8	
8-28-39	69	12,300	4.98	97	80	72-58	120-58	2800	15	10	10	10	2	

Complete rest in bed for eight days resulted in a remarkable recovery from the advanced cardiac decompensation on admission, as shown by the disappearance of his peripheral, pulmonary, and abdominal edema, a reduction of 17.4 Kg in weight, a fall in general venous pressure, a fall in general blood pressure and pulse, a reduction in cardiac size and in the size of the liver, and a slight decrease in total blood volume.

Following three weeks' rest in bed, the patient was considered ready for operation. Medication during this time, in preparation for operation, had been as follows: A high caloric, high vitamin diet, limitation of fluids to 1,500 cc daily, digitalis 0.6 Gm daily for two days, teleostol vitamin capsules two daily, betanin 10 mg daily, and mercopurin 2 cc intravenously on four occasions.

Operation—May 10, 1939 Cyclopropane anesthesia. Because of the large blood volume and the possibility that closure of the fistula might result in an overdistention of the cardiac chambers with consequent failure, the left thigh was draped to expose the saphenous vein for venesection and for the withdrawal of blood if necessary. Evidence of such overdistention would have been a fall in blood pressure and increase in pulse rate on closure of the fistula instead of the usual increase in blood pressure and fall in pulse rate. The inaccessibility of the fistula had prevented ascertaining the exact effect of closing the fistula before operation. The incision was made in the folds of the skin from

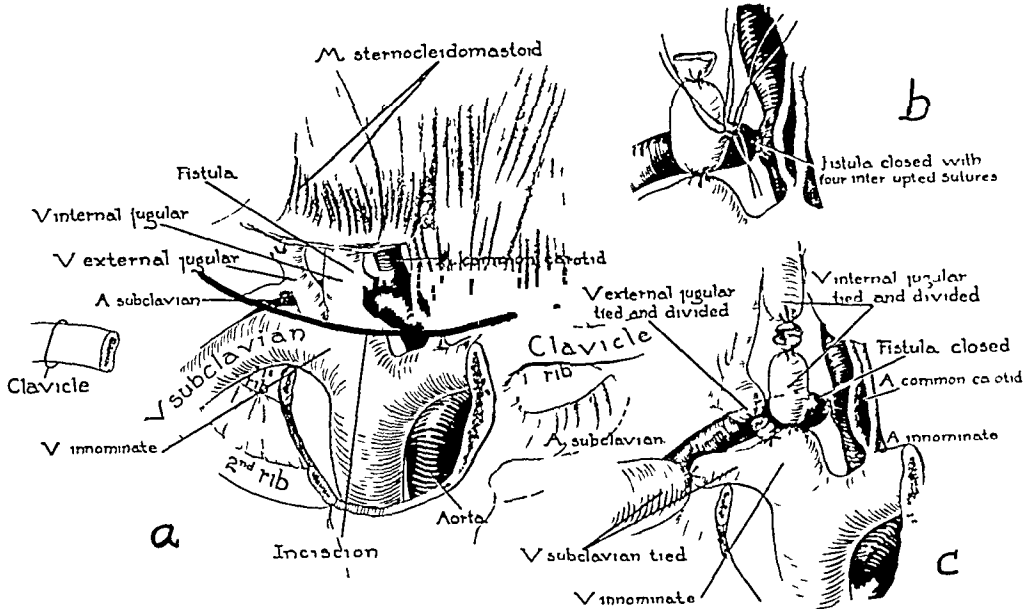


FIG 8—CASE 18. Conditions disclosed at operation for subclavian jugular fistula of six and one half years duration. Fistula eliminated by sutures in fistula itself by ligation of subclavian artery in its first portion by ligation of jugular vein distal and proximal to fistula, and by ligation of subclavian vein to balance the ligation of subclavian artery. No impairment of nutrition of the arm occurred.

the outer third of the clavicle to the left border of the sternum. A subperiosteal resection of the inner two-thirds of the clavicle was carried out. Scarring of the undersurface of the clavicle at the junction of the middle two-thirds indicated the site where the bullet had passed under the clavicle. The upper portion of the manubrium, together with the cartilaginous parts of the first and second ribs on the right, was removed. A hugely dilated innominate vein (Fig 8) was identified and partially isolated, but the extreme thinning of its walls made its complete mobilization hazardous. Arterial blood was seen swirling vigorously through this vein. The innominate artery was isolated for tape control if necessary, followed by mobilization of the subclavian artery in its first portion, and in its third portion. The jugular vein was isolated, ligated and divided in the mid-portion of the neck. Reflecting this vein and mobilizing it down to its junction with the subclavian vein revealed the fistula as a short 5 Mm wide tract running from the superior surface of the subclavian artery to the medial surface of the jugular vein (Fig 8). It was thought that a ligature could be applied to the fistulous tract if properly isolated, but in attempting to free it, the fibrous wall of the fistula was torn, causing a rather alarming hemorrhage which was controlled by digital pressure. The subclavian artery was then permanently ligated in continuity in its first portion with braided silk, as was

the jugular vein at its entrance into the innominate. The rents in the subclavian artery and in the jugular vein were completely closed by interrupted sutures of silk. Because of the permanent ligation of the subclavian artery, it was thought necessary also to ligate the accompanying vein. Accordingly, the subclavian vein in its third portion was ligated in continuity. The thrill, bruit, and bleeding were thus all effectively controlled. The wound was closed in layers. Despite the six-hour operation, the patient at the end of it was in excellent condition, pulse rate 84, blood pressure 102/70, whereas at the beginning of the operation the pulse rate was 90 and the blood pressure 110/60. Immediately following ligation of the subclavian artery, the pulse rate dropped from 106 to 82 and

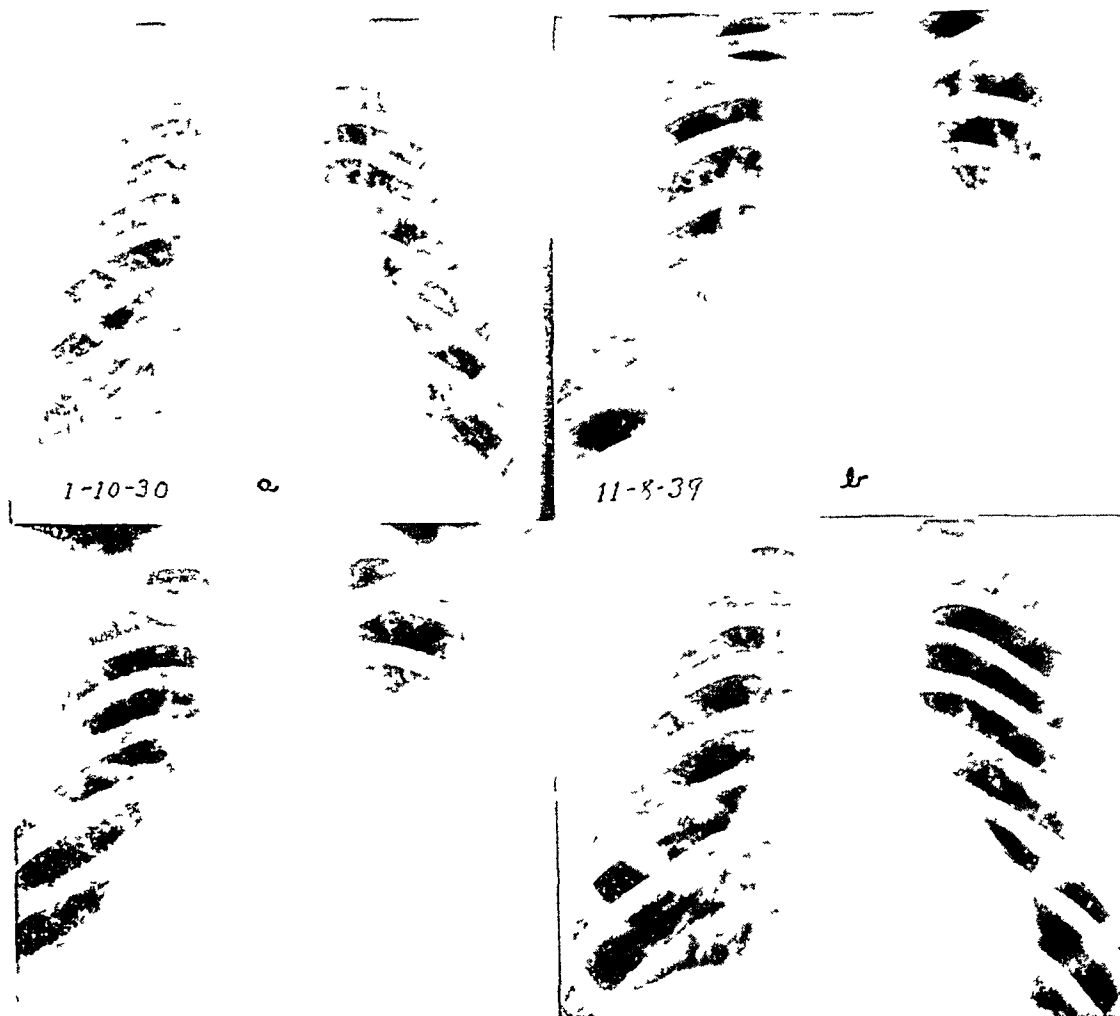


FIG 9—Case 19. Cardiac silhouettes in the presence of a popliteal fistula of ten years' duration. (a) At its inception. (b) In the presence of marked cardiac decompensation. (c) Following three weeks of complete rest there was no improvement. (d) Complete restoration to normal, two months following elimination of fistula.

the blood pressure rose from 90/60 to 120/74. No fluids were administered either during or after the operation, subcutaneously or intravenously. The closure of the fistula had the effect of providing a large autotransfusion of blood, thus accounting for the good condition of the patient.

One-half hour after his return to the ward a definite pulse could be felt in the right wrist, and at no time was there any apprehension about the circulation of the hand and arm. The blood pressure at this time was 114/74, pulse rate 80. There was a definite Horner's syndrome on the right, indicating that in the course of the operation the cervical sympathetics had either been severed or had been included in the ligatures. At 10 P.M., the hemoglobin had increased from a preoperative reading of 91 per cent to 100 per cent, and the red cells had increased from 5.1 million to 5.28 million, dropping again

the next morning to 93 per cent and 473 million. This temporary concentration of the blood elements is explained on the initial correction of the increased blood volume by an elimination of excess plasma. Two days after operation an icteric tint of the skin appeared, and his icterus index was 12, suggesting that the second correction of the increased blood volume was taking place, namely, a destruction of the red cells.

The patient rapidly recovered from his previous dyspnea and was discharged on the twelfth postoperative day, with instructions to remain in bed for two weeks while the previously hugely dilated heart recovered to normal size. He reentered the hospital, August 28, 1939, at which time he considered himself perfectly well. The Horner's syndrome was still present on the right. He had gained 12 pounds in weight since his operation in May. Other postoperative studies are recorded in Table III. The marked reduction in blood volume corroborated our experimental observations.

Case 19—W. J., male, age 24, was admitted to St. Luke's Hospital, November 7, 1939, with a swelling of the left leg and abdomen, shortness of breath, and anorexia of one month's duration. A letter from the San Francisco Hospital stated that the patient had been admitted to that hospital, December 23, 1929, with a gunshot wound of the left thigh. At that time a diagnosis of arteriovenous fistula was made. A roentgenogram, January 10 (Fig. 9a), showed that "the heart shadows were within normal limits, and the lung fields were clear." He was discharged, January 25. He was readmitted to the same hospital, February 17, 1930, at which time a diagnosis of arteriovenous fistula was again made, but he was discharged without the development of collateral circulation. His illness on admission to St. Luke's Hospital in November, 1939, was described as follows: One month previously the patient began to have sharp, sudden, stabbing pains in the left hypochondriac region, which were promptly followed by swelling of the ankles, legs, thighs, and abdomen. After two weeks in bed he attempted to get up, only to have the swelling reappear in his legs and abdomen. During the preceding three weeks he had been exceedingly short of breath until he was unable to sleep lying on his back. Only small amounts of food were eaten because of epigastric distress. Three weeks previously he also began to be troubled with a deep, tight, unproductive cough. The patient stated that since the gunshot wound in 1929 he had led a very active life, participating in many sports.

Physical Examination—Pulse 94, respirations 26, temperature 36° C, blood pressure 136/76. Chest showed absent breath sounds, dullness to percussion, and absent tactile fremitus over the entire left lower chest anteriorly and posteriorly. Breath sounds on the right were loud and hyperresonant to percussion, suggestive of a compensatory emphysema. The apex beat was 3 cm. outside the nipple line. There was a systolic thrill 2–3 cm. to left of nipple. Rhythm was irregular with a suggestion of gallop rhythm. There were no distinct murmurs. The abdomen was quite distended, with shifting dullness in the flanks (Fig. 10). He was tender throughout to deep palpation and particularly tender over the liver. Both legs showed extreme edema. There was a bullet scar on the medial surface of the left thigh 6 cm. above the knee, the wound of exit being 1 cm. lower on the posterolateral surface. There was a loud, coarse, continuous bruit heard over the entire left thigh, loudest immediately over the bullet scar on the medial surface. There was a distinct continuous thrill felt over this same area. Venous pulsations were observed in the lower leg and foot.

The patient stated that eight months previously he had been accidentally stabbed with a bayonet by a small boy, about 3 cm. above the left costal margin in the nipple line, the blade penetrating about 3 cm. Following this he had had pleurisy for a week with apparently no trouble thereafter.

On November 12, 1,420 cc. of yellow, clear fluid were removed from the left chest. In this fluid there were 625 white blood cells per cc. Revolta test was positive. Specific gravity was 1.013. This fluid was cultured and showed no growth. On November 28, 1,060 cc. of fluid were removed. On December 2, 250 cc. of bloody, turbid fluid were removed from the left chest. On December 11, 500 cc. of bloody fluid were removed. Following this



Fig. 10—Case 19 (a, b) Marked evidences of cardiac decompensation accompanying popliteal fistula of ten years' duration (c, d) Great improvement with complete rest in bed and frequent digital closure of artery proximal to fistula (e, f) Complete restoration to normal following elimination of fistula

last thoracentesis, the patient developed a high temperature. A pericardial friction rub could be heard throughout the cardiac cycle, and there was a pleural friction rub to be heard on inspiration in the third and fourth interspaces 2 cm to the left of the sternum. On November 15, despite one week's rest in bed, there were still a large amount of fluid in the abdomen, marked edema of the right lower leg, and even more edema of the whole left leg.

On November 20 the following observations as to general blood pressure and pulse were made. Fistula open, B P 138/90, pulse 92, immediately after closing fistula, B P 190/106, pulse 72, during the continued compression of the fistula, B P 150/100, immediately on opening the fistula, B P 110/60, with prompt recovery to 138/76. From this date until time of operation the fistula was closed three and four times daily for periods of ten to 20 minutes with the hope of reducing the amount of blood flowing through the fistula and enabling the tissues around the fistula to contract. Following this date, salivagan was administered three times—2 cc on November 23, 1 cc on November 26, and 1 cc on November 29. There was prompt improvement in many respects.

On November 1, his red cells numbered 3,900,000, white cells 10,000, and hemoglobin was 84 per cent. On November 22, red cells numbered 4,100,000 and hemoglobin was 78 per cent. On November 25, his red cells had increased to 5,000,000 and hemoglobin was 83 per cent. On December 26, the day before operation, the red cells numbered 4,300,000 and hemoglobin was 81 per cent. On January 3, the red cells numbered 5,500,000 and hemoglobin was 87 per cent. On January 7, red cells numbered 5,000,000 and hemoglobin was 84 per cent.

The following studies in vital capacity were made. On December 12, it was 1,650 cc, December 26, 2,620 cc (54 per cent of normal), January 10, after closure of the fistula, 4,300 cc (90 per cent of normal).

An electrocardiogram, November 10, showed the following. Pulse rate 100, p r interval 0.14 second, q r s normal, amplitude and duration slight right axis deviation.

By December 10, a remarkable diminution in the peripheral edema had occurred, in fact, the left thigh looked slightly smaller than the right, indicative of slight muscular atrophy. Seven inches above the upper border of the patella, the right thigh measured 18½ inches, the left thigh 18 inches. Nine inches below the upper border of the patella, the right lower leg measured 12½ inches, the left lower leg 13½ inches. A good pulse could be felt in the posterior tibial and dorsalis pedis arteries on both sides. On closing the fistula by digital compression, the posterior tibial pulse disappeared on the left, but the color of the foot remained good. With the fistula open, pulse was 96, blood pressure 118/72. On closing the fistula, blood pressure was 134/90, pulse rate 76. The tremendous increase in blood pressure obtainable on November 20, on closing the fistula, was conspicuously absent. On palpation the right femoral artery had an apparent diameter just below the inguinal ligament of 5/16 inch, the left femoral artery measured 10/16 inch in diameter. On the day before operation, the blood pressure was 130/76, pulse 86, with the fistula open, with the fistula closed the blood pressure was 142/86, pulse 80.

Operation—December 27, 1939. The patient was placed on his left side with the right thigh completely flexed on the abdomen. No tourniquet was used. A long incision was made paralleling the artery and the posterior border of the sartorius. The gracilis muscle was displaced posteriorly. The long saphenous nerve was mobilized and displaced posteriorly. The tendinous portion of the abductor magnus through which the artery passed was mobilized and divided in zigzag fashion. The artery and vein were hugely dilated down to the popliteal space. The fistula lay at the very apex of the popliteal space just 2 cm beyond the emergence of a very large anastomosis magna (Fig 11). The artery proximal to the fistula had a diameter of 1.8 cm, the vein proximal to the fistula was 2.2 cm in diameter. Beyond the fistula the artery was 9 mm in diameter, the vein 2 cm in diameter. Fortunately, it was possible to ligate the artery just beyond the anastomosis magna. A quadruple ligation was performed and the fistula excised. Following excision, a definite, though slight, pulsation could be seen in the stump of the

distal artery The proximal artery was ligated twice, first with a large braided silk, and secondly with a transfixion suture of medium silk

The following observations as to blood pressure and pulse were made during the operation Fistula open, B P 115/60, pulse 88, proximal vein closed B P 130/70, pulse 90, proximal vein reopened, B P 118/62, pulse 100, proximal artery closed, B P 122/70, pulse 70, artery open, B P 108/56, pulse 100, proximal artery and vein closed, B P 134/72, pulse 80 Following excision of the fistula, B P 130/74, pulse 90

Following the operation, the color of the left foot was good The B P at 1 00 P M

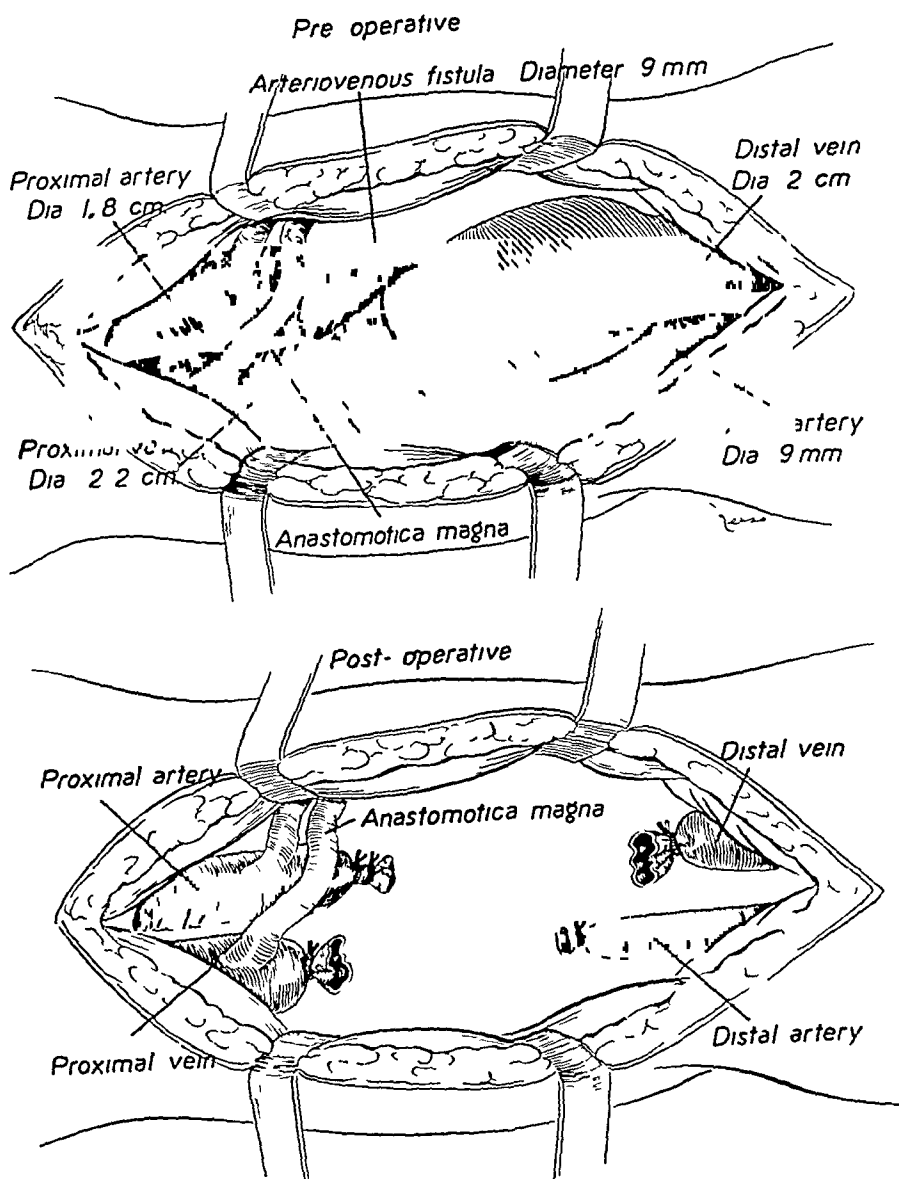


FIG 11—Case 19 Conditions found at operation for popliteal fistula of ten years' duration Marked dilatation of proximal artery Fistula eliminated by quadruple ligation and excision

was 110/70, at 2 00 P M, 122/82, at 3 00 P M, 122/82, at 4 00 P M, 112/70, at 5 00 P M, 110/68, at 6 00 P M, 124/84, at 8 00 P M, 116/86 On December 28, B P 134/82, pulse 80, on January 1, B P 140/90, pulse 70, on January 3, B P 140/90, pulse 80, and on January 8, B P 134/96, pulse 80 On January 8 the apparent diameter of the left femoral artery was 9/16 inch, right femoral artery 6/16 inch The circumference of the lower leg, nine inches below the upper border of the patella, was 12½ inches on the left and 12 inches on the right The circumference of the thigh, seven inches above the upper border of the patella, was 16½ inches on the left and 16½ inches on the right

The wound healed *per primam* The patient was allowed out of bed, January 10, and was discharged from the hospital, January 14, 1940

Case 20—B C, age 15, entered Stanford Hospital, June 14, 1939, for an arterio-

venous fistula of the left brachial vessels following an accidental gunshot wound ten weeks previously. The 22-caliber bullet entered the left upper arm two and one-half inches below the axillary fold on the medial surface, and emerged posteriorly, miraculously avoiding the bone. Severe bleeding occurred, but by the time the boy reached the hospital, one and one-half hours later all external bleeding had ceased. The arm itself, however, promptly swelled to twice its normal size. As this swelling slowly disappeared, during the following four weeks, the patient noted a gradually increasing thrill over the site of the injury. He also noted an increased pounding of his heart, particularly when

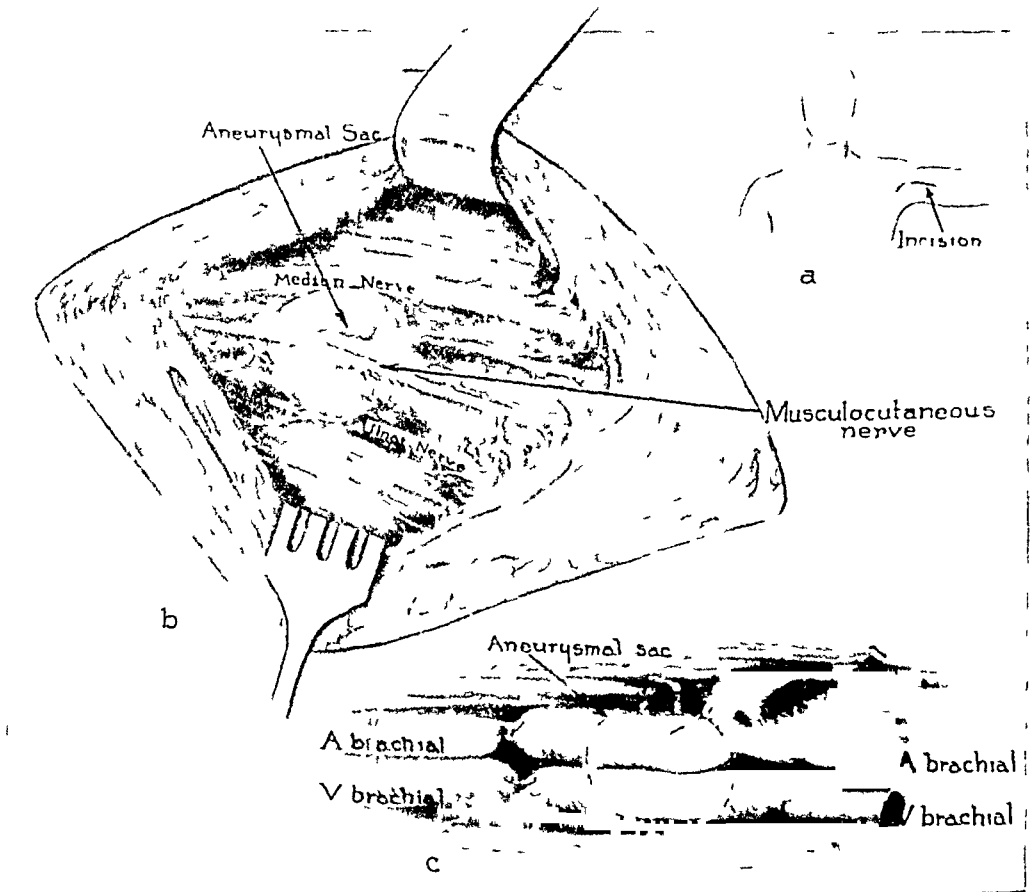


FIG 12—Case 20 Conditions at site of brachial fistula of ten weeks duration. Quadruple ligation in continuity to avoid any possible injury to closely lying nerves.

he lay quietly in bed. There were no other symptoms. He had been able to play tennis without dyspnea.

Physical Examination—The patient was a robust, healthy appearing young man. The left upper arm was slightly larger than the right, a loud bruit could be heard over the brachial vessels extending down toward the elbow, and upward as far as the base of the heart. There was no distention of veins. The heart was slightly enlarged, the apex beat being 2 cm outside the nipple line in the fifth interspace. The thrill and bruit were easily stopped by pressure over the site of injury, the closure of the fistula being accompanied by a rise in blood pressure from 112/70, pulse 84, to 122/84, pulse 63. A pre-operative total blood volume of 6,360 cc was determined, which was approximately 600 cc greater than would be predicted from his weight of 64.1 Kg and his surface area of 1.74 sq M. The consistent increase in blood pressure and fall in pulse rate on closing

ARTERIOVENOUS FISTULAE

the fistula were interpreted as indicating a large fistula that would not heal spontaneously, and operative elimination of the fistula was advised

Operation—June 16, 1939 Under gas anesthesia, a longitudinal incision was made over the brachial vessels. Considerable matting together of all structures, including the vessels themselves, the median, ulnar, and musculocutaneous nerves (Fig 12a), made identification of structures difficult, but by working *without* a tourniquet the pulsating artery and full vein rendered the isolation of these structures easier. The musculocutaneous nerve lay flattened out immediately over a small aneurysmal swelling projecting from

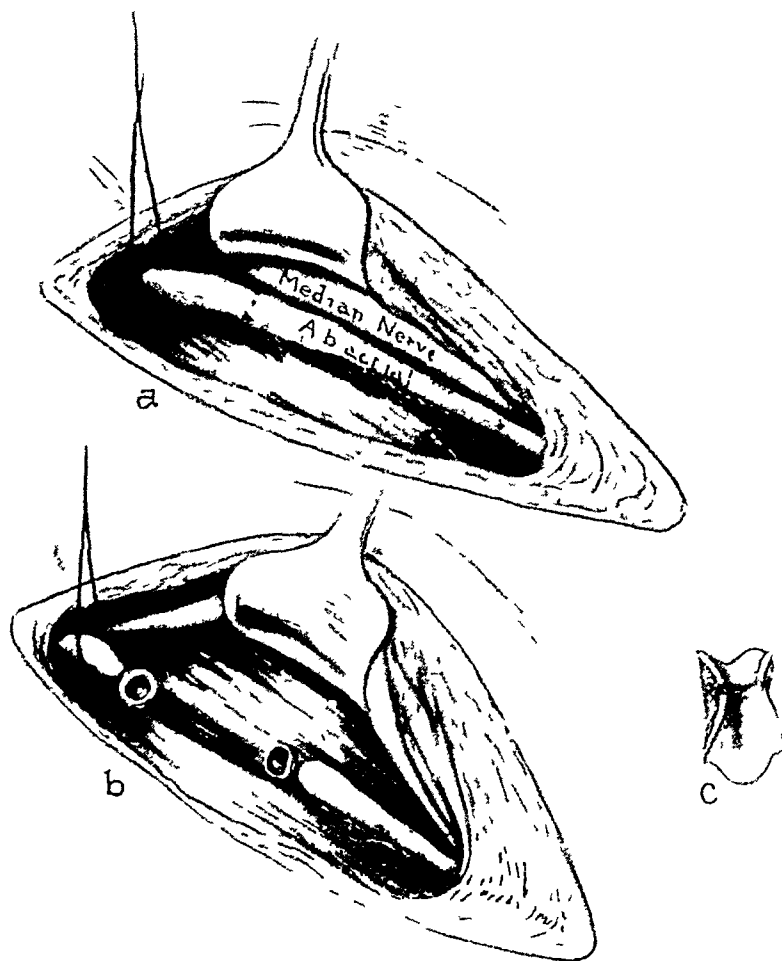


FIG 13—Case 20. At the second operation, following reactivation of the brachial fistula, it was found that the lumen of the brachial artery, proximal to the fistula, had been reestablished by the ligature cutting through the arterial wall providing a lumen $3\frac{1}{2}$ Mm in diameter, the original artery having a diameter of 10 Mm. Simple excision of the previous ligature and ligation cured the fistula.

the vein. The proximal artery was dilated to 1 cm in diameter, the distal artery having a diameter of only 3 Mm. Because of the matting together of the nerves and vessels, particularly in the region of the fistula, it was decided to perform a quadruple ligation of the vessels in continuity, and not to excise the fistula for fear of severing important nerve fibers. Following ligation of the four cardinal vessels with silk, all evidences of the fistula were absent. The wound was closed without drainage. At the operating table, just before closing the fistula, B P was 138/60, pulse 84. Following ligation of the vessels, B P rose to 144/80, pulse 76. The following day, B P 136/86, pulse 68. On the sixth postoperative day, B P 130/70, pulse 72. Healing *per primam* occurred, and the

patient was dismissed from the hospital on the tenth postoperative day, apparently cured of his fistula, and with a fair radial pulse Six days following the operation a total blood volume of 6,000 cc was found

Exactly three weeks after the operation, he was again examined, and to our utter amazement (and chagrin) a thrill and bruit were again present Pressure on the pulsating artery proximal to the site of the fistula caused the bruit to disappear Localized pressure with a small pad over this vessel for several weeks did not affect the bruit Accordingly, on August 22 the wound was reopened and to our surprise the silk ligature was found to have partially cut through the wall of the artery proximal to the fistula, reestablishing the lumen of the vessel and, thereby, reactivating the fistula (Fig 13) The vessel was again ligated, and the segment containing the previous ligature excised Complete and permanent disappearance of the thrill and bruit followed The lesson is obvious When performing quadruple ligation in those instances where excision of the fistula may not be feasible or desirable, the main proximal artery should be ligated not in continuity but ligated and divided

Blood pressure studies were again instructive On admission 108/60, pulse, 76, two hours following religation of brachial artery 124/70, pulse 70, first day postoperative 124/74, pulse 82, second day postoperative 130/76, pulse 70, third day postoperative 130/80, pulse 70, fourth day postoperative 120/66, pulse 80

Case 21—B P, colored, male, age 10, was admitted to the San Diego General Hospital, August 13, 1939, 24 hours after an accidental gunshot wound of the left groin, the 22-caliber bullet entering at a point midway between the symphysis and the anterior superior spine about one inch above the inguinal ligament and emerging in the gluteal fold of the left buttock Only a minimal amount of bleeding occurred On examination, 24 hours after the accident, there was but little local swelling, the wounds of entrance and exit were small and closed, but a palpable thrill and audible bruit were most pronounced over the site of injury The heart measured 11.7 cm in transverse diameter Red blood cells numbered 2,250,000, hemoglobin 67 per cent He was discharged August 22, the thrill and bruit being still present

On readmission, September 15, the heart had increased to 12.5 cm in diameter, there was now a soft systolic murmur audible over the entire precordium, which was absent before The red cells now numbered 3,330,000, hemoglobin 56 per cent The thrill and bruit were, if anything more audible than before He was discharged, October 3

On November 9, he was readmitted for operation, which was performed by me and Dr Thomas O'Connell, November 15 Preoperative studies demonstrated a heart still enlarged, with the systolic murmur still present over the entire precordium The red cells numbered 4,820,000, hemoglobin 88 per cent A total blood volume of 2,875 cc was determined Blood pressure was 122/60, pulse 90 On closing the fistula by compression, the blood pressure increased to 130/80, pulse 80

Operation—November 15, 1939 A curved incision was made paralleling the inguinal ligament for about 10 cm and then continuing down the inner aspect of the thigh for 6 cm (in order to avoid crossing the creases of skin in the groin), the common femoral artery and vein were first isolated for temporary closure if necessary As the dissection of these vessels was carried distally, it was found that the fistula lay between the common femoral artery just opposite the deep femoral branch and the superficial femoral vein Its excision was accomplished (with considerable difficulty due to deep venous bleeding requiring several transfusion sutures) by ligation of the common femoral artery, the deep femoral artery, and the superficial femoral artery, and by ligation of the superficial femoral vein proximal and distal to the fistula, and the deep femoral vein Before ligation, the common femoral artery measured 9 Mm in diameter, the superficial femoral artery 4 Mm, and the deep femoral artery 2 Mm In the excised state, the common femoral artery measured 4 Mm in diameter, and the fistulous rent in the artery 4 Mm in diameter One may infer, therefore, that in the distended, or living state, the fistula had a diameter approximately equal to the size of the artery, or about 9 Mm

Following excision of the fistula, the pulse dropped from 130 to 104. One hour after the operation, the pulse was 130, blood pressure 124/50. Twenty-four hours later the blood pressure was 118/82. A rapid diminution in the size of the heart occurred, its transverse diameter on November 24 being 10.6 cm, as compared to a preoperative diameter of 12.3 cm. A total blood volume determination showed a decrease of 300 cc following removal of the fistula. The wound healed *per primam*, and at no time was there any doubt of the adequacy of the circulation of the extremity, which is rather extraordinary, considering the number of large vessels ligated. The reason, undoubtedly, lies in the stimulus to collateral circulation provided by the decreased peripheral resistance at the site of the fistula.

SUMMARY OF CLINICAL OBSERVATIONS

In analyzing these clinical experiences, the following points may be emphasized:

(1) Complete cardiac decompensation with peripheral edema, ascites, hydrothorax, and extreme dilatation of the heart may be completely corrected with return of the heart to normal size by the elimination of a peripheral fistula (Cases 18 and 19). This dilatation involves not only the heart but the great vessels at the base of the heart as well, as demonstrable by roentgenograms before and after elimination of the fistula (Cases 15, 16, 18, 19).

(2) Early evidence of the malign influence of a fistula upon the circulation—even before dilatation of the heart is detectable—is the behavior of the blood pressure and pulse following closure of the fistula by digital pressure. An increase in blood pressure and a fall in pulse rate, even though both are small, indicates that the fistula is large and is one which is not likely to close spontaneously, but is almost certain to produce increasing deleterious effects upon the circulation (Cases 13 and 17). In Case 18, failure to heed this evidence, first in 1933, when the heart was normal, and again in 1936, when the heart was beginning to dilate, led to a complete cardiac failure with great cardiac dilatation in 1939.

(3) This increase in blood pressure and fall in pulse rate is the first evidence that the circulatory bed through which the short-circuited blood flows is beginning to dilate, even though such dilatation may not yet be detectable by the usual means.

(4) The extent of the increase in blood pressure and fall in pulse rate depends upon the duration of the fistula, and is commensurate with the extent of the dilatation of the heart and vessels proximal to the fistula, being least in the fistulae of short duration with no or slight cardiac dilatation (Cases 13, 14, 17, 20 and 21), and greatest in the fistulae of long duration with great cardiac dilatation (Cases 15, 16, 18 and 19).

(5) A temporary but great increase in blood pressure and fall in pulse rate may occur immediately following the elimination of a fistula by operation, provided the operation is performed as a physiologic experiment without loss of blood (Cases 15 and 16). Despite prolonged operations, 4–6 hours long, the blood pressure at the end of the operation was higher and the pulse slower than at the beginning, due to an auto-transfusion from circulating blood which had increased in volume during the presence of the fistula (Cases 15, 16, 17, 18, 20).

(6) This temporarily great increase in blood pressure and fall in pulse rate on closing a fistula are dependent upon an increase in total blood volume, which is an inevitable accompaniment of a fistula of large size and long duration. In Case 15 the blood volume dropped from 7,200 to 6,200 cc after the removal of the fistula and in Case 16, the blood volume dropped from 5,000 cc to 4,200 cc after elimination of the fistula. Both cases showed marked cardiac dilatation and marked effects upon blood pressure and pulse, upon closing the fistula. A less marked effect on blood pressure and pulse occurred



FIG 14—Animal 8. Roentgenograms of heart following establishment of an aorta-vena cava fistula. (a) 10:45 A.M., just before opening the fistula. (b) 11:15 A.M., 15 minutes after opening fistula. (c) 1:30 P.M. (d) 4:00 P.M. At 6:1 P.M. the animal died as the result of the fistula.

in Cases 20 and 21, in which the blood volume was reduced only 300 cc in each case following elimination of fistulae of short duration. In case 18, blood volume was reduced from 8080 cc to 7560 cc by correction of the cardiac decompensation and from 7560 cc to 5375 cc by elimination of the fistula.

(7) The increased blood volume is reduced immediately following operative removal of a fistula by a reduction in the plasma as shown by increased urinary output (Case 16), and by a concentration of the red cells and hemoglobin in the blood (Cases 15, 16, 17 and 19). In Case 21, a marked dilution of blood followed the establishment of the fistula which was gradually corrected to practical normal figures.

(8) This increased blood volume may result in a transient overdistention of an already dilated heart following closure of a fistula by operation, due to a redistribution of the circulating blood, the volume of blood formerly diverted through the fistula into the capacious venous system now filling the central arterial bed (Cases 15 and 16)

(9) Eight cases of peripheral fistulae were eliminated by excision or ligation of segments of the main vessel to a limb without any evident effect upon the viability of the tissues beyond the ligation. In Case 21, the common femoral, deep femoral, and superficial femoral arteries were all ligated

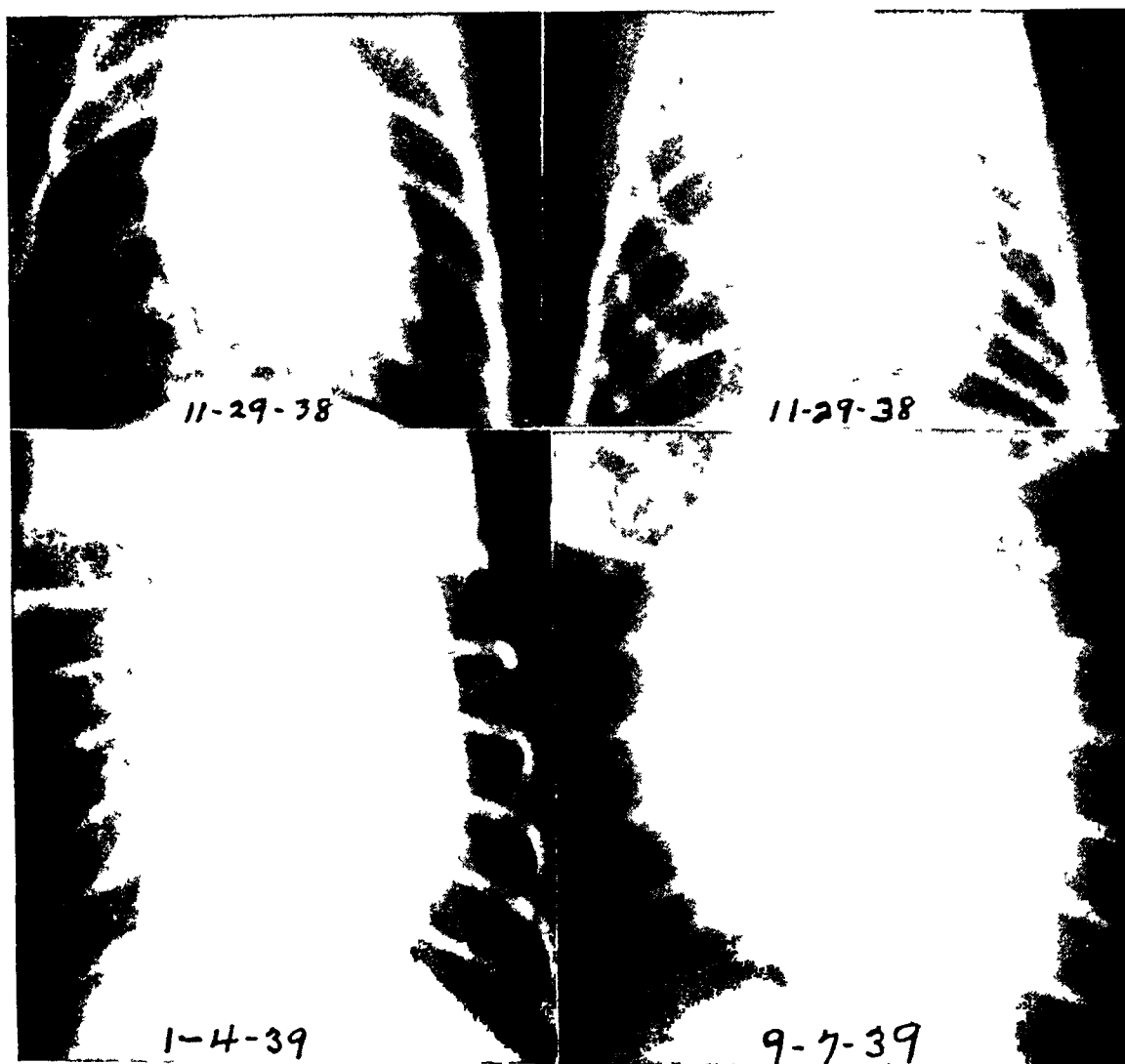


FIG 15—Pup 1. Variations in cardiac silhouette in animal that survives production of an aorta-vena cava fistula—an initial decrease in size is quickly supplanted by dilatation

without impairment of nutrition or function of the leg. This is explicable on the basis of the stimulus to collateral circulation provided by the area of diminished peripheral resistance at the site of the fistula, which attracts blood to it through all available channels.

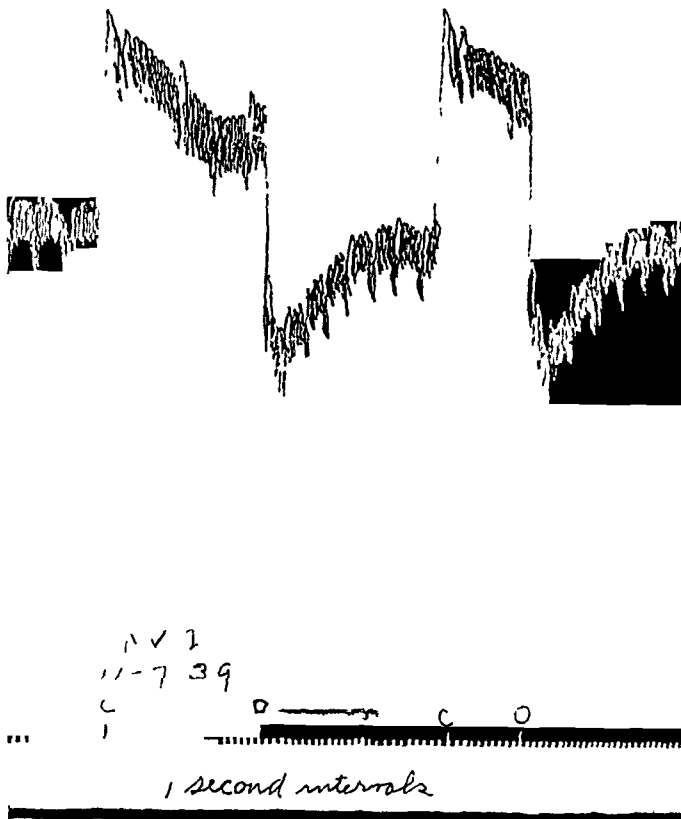
(10) When quadruple ligation of the vessels proximal and distal to the fistula is indicated, it would be desirable to ligate and divide the artery proximal to the fistula rather than to ligate it in continuity. In Case 20, the fistula was reactivated by the ligation cutting through the arterial wall and thereby reestablishing the lumen of the artery.

EXPERIMENTAL OBSERVATIONS

Animal 8—Female, adult dog, weight 9 Kg. An aorta-vena cava fistula was established, January 24, 1939 aorta 6.5 Mm in diameter, venr cava 8.5 Mm in diameter, fistula 5.5 Mm long. Before opening the fistula (10 45 A M) a roentgenogram of the chest was taken—pulse 120. At 11 15 A M a second roentgenogram showed a slight diminution in cardiac size—pulse 120. At 1 30 P M the cardiac size was even smaller—pulse 132—and at 4 00 P M the heart was remarkably smaller—pulse 200 (Fig. 14). At this time there was marked edema of both lower extremities. The animal died at 6 P M two hours later.

Pup 1—Male weight 9 Kg. On November 29, 1938 an aorta-vena cava fistula was established aorta 6 Mm in diameter venr cava 8 Mm in diameter, fistula 5 Mm long. The pulse rate was immediately accelerated from 120 to 172 on opening the fistula.

According to roentgenograms (Fig. 15), a slight diminution in the cardiac shadow occurred immediately after the opening of the fistula, but within 24 hours the heart had recovered its original size followed in the succeeding months by a truly enormous enlargement of the heart. At all times after the establishment of the fistula, good femoral pulsations were present on both sides. On April



GRAPH 1—Pup 1. Kymographic record showing marked elevation of blood pressure and reduction in pulse rate on closing an aorta-vena cava fistula of 11 months' duration. Blood volume in this pup was 1,550 cc as compared to 960 cc in litter mate control.

24, 1939, the pulse rate was 192, respirations 52 the heart was very much enlarged and there was great dyspnea on exertion. On November 7, 1939 the animal was in much better condition, there was no edema, no ascites, good femoral pulsations were palpable, large veins were visible over the abdominal wall and a loud bruit was audible over the lower abdomen. On this date, approximately one year after the establishment of the fistula, the carotid artery was cannulized to obtain a continuous record of the blood pressure. The fistula was exposed and closed by compression. Immediately there was a most pronounced increase in blood pressure and a fall in pulse rate (Graph 1). Analyzing this kymographic record, we find that closure of the fistula increased the mean systolic pressure from 186 to 236 Mm Hg, immediately after closing the fistula, dropping to a level of 212 Mm Hg as long as the fistula remained closed, falling precipitately on opening the fistula to 140 Mm Hg, but recovering promptly within a few beats to the previous level of 186 Mm Hg. Variations in pulse rate paralleled these changes in blood pressure. The animal was killed, and examination revealed an aorta dilated from the heart to the fistula and a greatly dilated venr cava from the fistula to the heart. The heart almost filled the chest. The fistula admitted a bougie having a circumference of

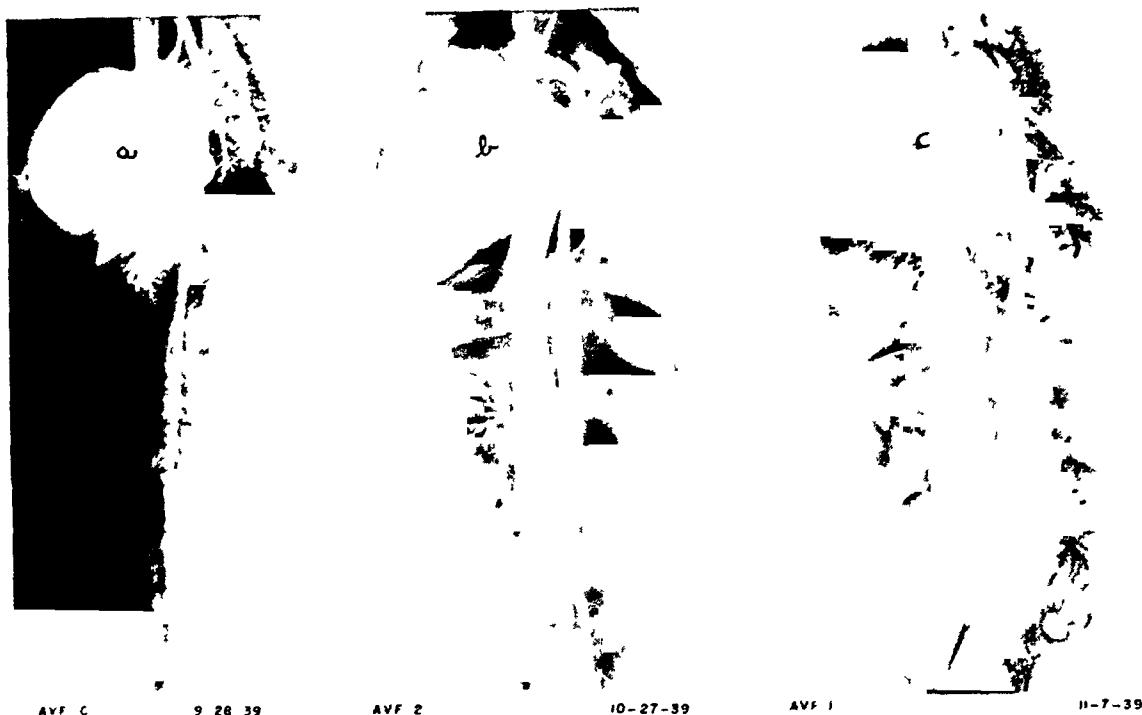


FIG 16—Roentgenograms of three litter mates following injection of circulatory system with bismuth oxychloride (a) Normal heart, aorta, and vena cava of control animal (b) Moderate dilatation of heart, aorta, and vena cava following establishment of aorta vena cava fistula, which at death proved to be 12 Mm in circumference (c) Great dilatation of heart, aorta, and vena cava incident to fistula 18 Mm in circumference These injections prove that the dilatation involves the entire circulatory system through which the short circuited blood passes, namely, the aorta from heart to fistula, the vena cava from fistula to heart, and all chambers of the heart



FIG 17—The dilatation of the heart is commensurate with the size of the fistula (a) Heart of control dog, weight 74 Gm (b) Heart of Pup 2 with an aorta vena cava fistula 12 Mm in circumference, weight 123 Gm (c) Heart of Pup 1 with an aorta vena cava fistula 18 Mm in circumference, weight 176 Gm

All animals from the same litter and approximately equal in size and weight

18 Mm The circulatory system was injected with bismuth oxychloride in gum arabic (Fig 16) The heart weighed 176 Gm, weight of animal 111 Kg (Fig 17)

Pup 2—Male weight 83 Kg On December 6, 1938 an aorta-vena cava fistula was established aorta 5 Mm in diameter, vena cava 8 Mm in diameter On opening the fistula the pulse rate rose from 132 to 160 On the following day a good pulse could be palpated in both femoral arteries there was no edema, and the pulse rate was 180 A roentgenogram taken 24 hours after establishing the fistula showed a definite decrease in the size of the heart On December 8, 1938, the heart had recovered its previous size, there was a good femoral pulse to be felt in both groins, and the pulse rate was 200 The animal continued in good health until October 27, 1939 On this date, the heart had increased greatly in size although not as much as the heart of the litter mate The pulse rate was 140 A good femoral pulse could be felt on both sides and there was no edema The fistula was exposed and compressed causing a fall in pulse rate from 140 to 104 The animal was killed and the circulatory system injected with bismuth oxychloride in gum arabic The aorta and vena cava were both dilated from the fistula to the heart (Fig 16) and the heart was greatly enlarged The heart weighed 123 Gm, weight of animal 100 Kg (Fig 17) From the lesser cardiac enlargement as compared with Pup 1, it was considered probable that the fistula was smaller in this animal than in Pup 1 This proved to be the case The fistula admitted a bougie having a circumference of 12 Mm as compared with 18 Mm in Pup 1

The control animal was also killed on this date and the heart and circulatory system injected with bismuth oxychloride (Fig 16) The heart weighed 74 Gm, weight of the animal 116 Kg (Fig 17)

The following observations on total blood volume in these three litter mates were made

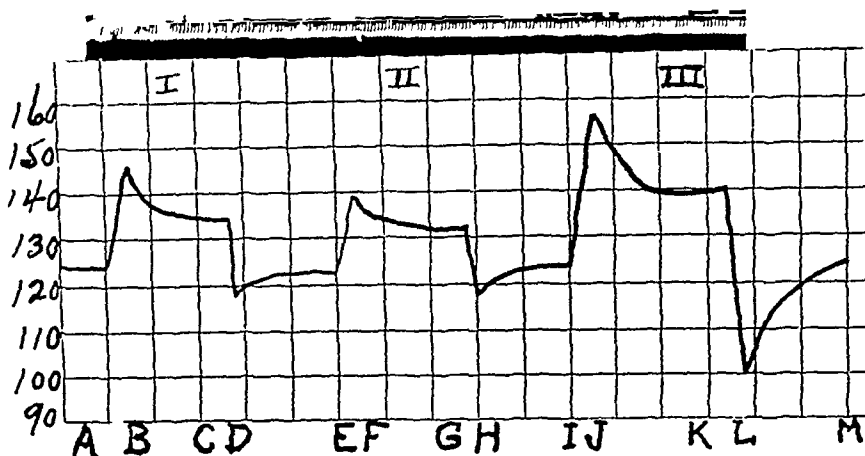
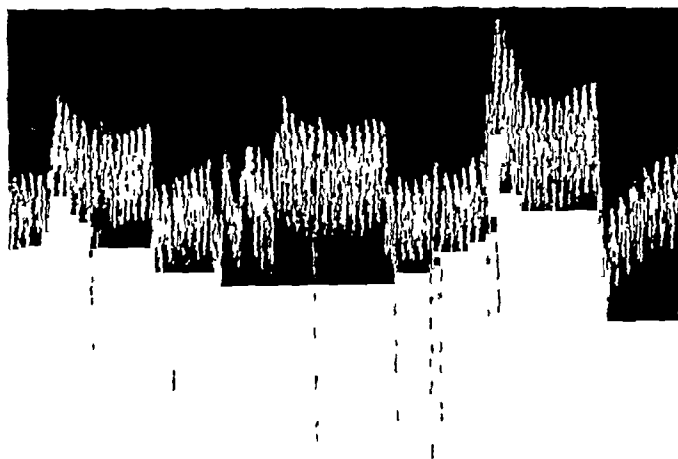
Animal	Dates	Weight	Blood Volume
Control	2/23/39	104 Kg	950 cc
	8/23/39	116 Kg	960 cc
Pup 2	2/28/39	105 Kg	1,190 cc
	9/20/39	107 Kg	1,210 cc
Pup 1	2/23/39	100 Kg	1,430 cc
	8/23/39	111 Kg	1,550 cc

By mathematical computation from measurements obtained in the roentgenograms of the injected animals (Fig 16), the following approximate capacities were determined for that part of the circulatory system included in the shorter fistulous circuit, including the heart, the aorta from heart to fistula, and the vena cava from fistula to the heart

	Capacity	Total Blood Volume	Increase in Capacity as Compared to Control	Increase in Total Blood Volume as Compared to Control
Control	200 cc	960 cc		
Pup 2	480 cc	1,210 cc	280 cc	250 cc
Pup 1	775 cc	1,550 cc	575 cc	590 cc

In these three litter mates, equal in weight and stature, there was a surprising correlation between the increase in capacity of the shorter circuit and the increase in the total blood volume, both being commensurate with the size of the fistula It may be inferred that if no demonstrable dilatation of the heart or of the vessels proximal to the fistula occurs, there is probably also no demonstrable increase in blood volume I believe that even small fistulae are accompanied by a minor dilatation of the heart and vessels and by commensurate increases in total blood volume, but our methods are not exact enough and our eyes not keen enough, to demonstrate, and to recognize, such minor dilatations and such small increases in blood volume It is freely granted that

the dye method is not an absolutely accurate method of studying blood volume, but one cannot ignore these results obtained in animals of the same litter on successive occasions, nor can one escape the fact that if there is a considerable increase in the capacity of the circulatory system by dilatation, there must be an increase in blood volume to fill it



GRAPH 2—Kymographic record of carotid blood pressure in the presence of bilateral femoral fistulae (A) Both fistulae open, pulse 102 (B-C) Right fistula closed, pulse 87 (D-E) Both fistulae open, pulse 98 (F-G) Left fistula closed, pulse 82 (H-I) Both fistulae open (J-K) Both fistulae closed simultaneously, pulse 76 (L-M) Both fistulae opened simultaneously. The effect upon blood pressure and pulse depends upon amount of blood diverted into the venous bed

The Effects of Bilateral Femoral Fistulae on Arterial Pressures—In an animal in which bilateral femoral fistulae had been established, October 31, 1934, the following observations (Graph 2) were made, June 28, 1938. Under nembutal anesthesia, and with aseptic precautions, the right carotid artery was cannulized and both fistulae in the groin were exposed to permit complete closure of the artery proximal to the fistula. On closing the right fistula, the blood pressure rose immediately from 124 Mm Hg (pulse 102) to 146 Mm Hg, dropping to a level of 136 Mm Hg (pulse 87) as long as the fistula remained closed. On opening the fistula the blood pressure dropped precipitately to 118 Mm Hg, rising promptly to a level of 122 Mm Hg as long as

the fistula remained open. Similar figures were obtained on closing the left fistula (Graph 2). On closing both fistulae simultaneously, the pressure rose precipitately to a high point of 156 Mm Hg (pulse 76), dropping to a level of 140 Mm Hg as long as the fistula remained closed. On opening the two fistulae simultaneously, the pressure dropped to a low point of 100 Mm Hg for several beats only, rising promptly to the previous level of 124 Mm Hg.

This was a convincing demonstration of the fact that the physiologic effects of opening and closing a peripheral fistula depend upon the volume of blood escaping into the shorter circuit.

The Effects of Bilateral Femoral Fistulae on Vena-Caval Pressures—On April 14, 1939, the animal in which bilateral femoral fistulae had been established three and one-half years previously was again subjected to nembutal anesthesia and under aseptic precautions the following procedures were carried out. Through an incision in the flank the right kidney was mobilized, the renal artery was ligated, and a glass cannula, connected with an upright glass tubing of equal caliber, was inserted into the vena cava through the renal vein. The pressure, oscillating with respiration, was recorded in centimeters of water under the following conditions:

	Vena-Caval Pressure in cc of Water Varying with Respiration					
Both fistulae open	12	-13	17	-18	19	-20
Right fistula closed					16	5-17
Left fistula closed	10	-11	15	-16		
Both fistulae closed	8	5-9	12	-13	15	-15.5
Both fistulae open	12	5-13	15	5-16	5	18 5-19

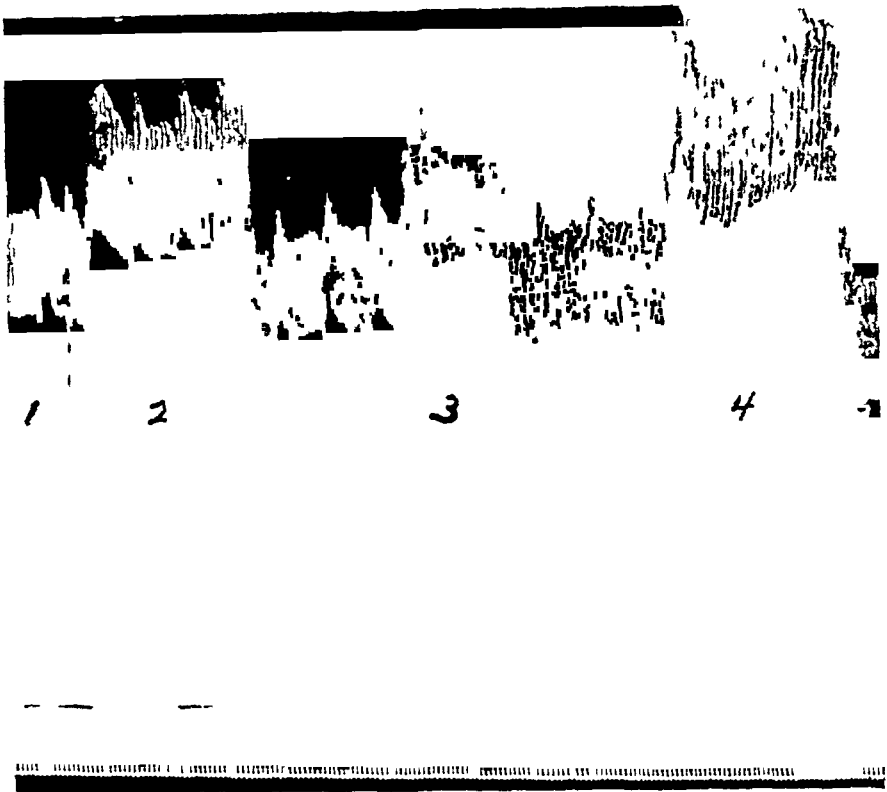
It was apparent, from observation, that the vena cava was able to accommodate much of the increased volume of blood transmitted through the fistula under arterial pressure by an increased velocity of flow. However, it was also apparent that the vena-caval pressure varied directly with the volume of blood diverted through the fistulae, being greatest with both fistulae open, least with both fistulae closed, and intermediate rises in vena-caval pressure occurred as one or the other fistula was opened separately.

On March 19, 1940, a second dog (Animal 3), in which bilateral femoral fistulae had been established on June 30, 1938, was investigated as to vena-caval pressures. Under morphine and ether, a long glass cannula was introduced through a rent in the left external jugular vein down into the thoracic vena cava. This experiment differed from the preceding experiment in that both the abdomen and the thorax were intact. The following observations were noted, the vena-caval pressures oscillating 5 to 10 Mm with respiration:

	Vena-Caval Pressure in cc of Water	Pulse
Both fistulae open	9 5-10	108
Right fistula closed	6 5-7	90
Left fistula closed	7 5-8	96
Both fistulae closed	5 5-6	88
Left fistula reopened	7 5-8	
Both fistulae open	9 5-10	5

Again it was demonstrated that vena-caval pressure was increased in the presence of bilateral femoral fistulae, the greatest increase occurring when both fistulae were open. Closing one or the other fistula lowered the venous pressure 2-3 cc, whereas closure of both fistulae simultaneously lowered it 4 cc.

On March 4, 1940, the dog in which two femoral fistulae had been established on October 31, 1934, was again anesthetized, the remaining left renal vein was cannulized for vena-caval pressures, and the remaining left carotid



Conditions at Site of Fistulae	Mean Arterial Pressures Carotid Artery mm Hg	Vena Caval Pressures cm H ₂ O
1 Both Open	136	13 - 15
2 Left Closed	160	9 - 10.5
3 Right Closed	156	8.5 - 10
4 Both Closed	182	6 - 7
5 Both Open	120	13 - 14

GRAPH 3—Kymographic record of carotid arterial pressures dependent upon conditions at site of bilateral femoral fistulae of five and one half years' duration. Vena caval pressures obtained by cannulization of renal vein.

artery was cannulized for arterial pressures (Graph 3). It is evident from the kymographic record that when both fistulae were open the vena-caval pressure was high, and carotid pressure was low, when both fistulae were closed, vena-caval pressure was low and carotid pressure was high. Intermediate arterial and vena-caval pressures were obtained depending on closure of one or the other fistula.

From these many observations one may conclude (1) That a rise in venous pressure occurs proximal to an arteriovenous fistula, and (2) that the extent of this rise in venous pressure depends upon the amount of blood diverted into the shorter circuit, and, therefore, upon the size of the fistula

SUMMARY OF EXPERIMENTAL OBSERVATIONS

In the first 24 to 48 hours after the establishment of a large arteriovenous fistula, the heart diminishes in size, followed, if the animal survives, by a prompt return to normal, and, subsequently, by a gradual dilatation which may be apparent within four to five days

Death, due to an excessive diversion of blood through the fistula, may occur, accompanied by a marked diminution in cardiac size

The dilatation that accompanies an arteriovenous fistula is not restricted to the heart, but affects the vessels involved in the fistulous circuit. The same cause is responsible for both dilatations, an increase in the volume or bulk of blood flowing through that part of the circulatory system through which the blood short-circuited by the fistula must flow, namely, all the chambers of the heart, the proximal artery, fistula, and the proximal vein

In the growing animal, the dilatation and enlargement may be very great without evidence of decompensation and may be accompanied by pronounced hypertrophy. It is suggested that when dilatation outstrips hypertrophy decompensation occurs, when dilatation is paralleled by a commensurate hypertrophy, great enlargement and dilatation of the heart may occur without decompensation

In a crucial experiment, involving three litter mates of equal weight and stature, one acting as control, one having an aorta-vena cava fistula 12 Mm in circumference, and one having an aorta-vena cava fistula 18 Mm in circumference, there occurred an increase in blood volume commensurate with the size of the fistula

In the same animals, an increase in the capacity of the circulatory system occurred, also commensurate with the size of the fistula. The increase in capacity and the increase in blood volume closely paralleled each other

In an animal with bilateral femoral fistulae the increase in blood pressure and reduction in pulse rate were greatest when both fistulae were closed simultaneously, and considerably less when either fistula was closed separately. The physiologic effect of a fistula therefore, clearly depends upon the volume of blood diverted through the fistula and, therefore, upon its size

The transient high systolic and diastolic pressures that persist for several days following operative closure of a fistula are due to the increase in blood volume that has occurred during the existence of the fistula. The permanent elevation of diastolic pressure is secondary to the elimination of an area of decreased peripheral resistance

In animals having bilateral femoral fistulae, vena-caval pressures were highest with both fistulae open, least with both fistulae closed, and interme-

diate pressures were obtained on closing one or the other fistula separately. Venous pressures proximal to a fistula are determined by the volume of blood diverted through the fistula and, therefore, by the size of the fistula.

REFERENCES

- ¹ Lewis, T. and Drury, A. N. Observations Relating to Arteriovenous Aneurysm Heart, 10, 301, 1923
- ² Harrison, T. R., Dock, W., and Holman, E. Experimental Studies in Arteriovenous Fistulae. Cardiac Output Heart, 11, 337, December, 1924
- ³ Quattlebaum, J. T. Arteriovenous Aneurysm Amer Heart Jour, 13, 95, January, 1937
- ⁴ Reid, Mont R., and McQuire, J. Arteriovenous Aneurysms ANNALS OF SURGERY, 108, 643, October 1938
- ⁵ Green, H. D. Coronary Blood Flow in Aortic Stenosis, Aortic Regurgitation and in Arteriovenous Fistula Am Jour Physiol, 115, 94, 1935
- ⁶ Holman, Emile. The Physiology of an Arteriovenous Fistula Arch Surg, 5, No 7, 64, July, 1923
- ⁷ Holman, Emile. Observations on the Surgery of the Large Arteries ANNALS OF SURGERY, 85, No 2, 173, February, 1927
- ⁸ Holman, Emile. Arteriovenous Aneurysm ANNALS OF SURGERY, 80, 801, December, 1924
- ⁹ Holman, Emile. Arteriovenous Aneurysm Surg Clin North Amer, 8, No 6, 1413, December, 1928
- ¹⁰ Holman, Emile, and Shen, J. K. The Application of the Matas Principle of Endo-Aneurysmorrhaphy in the Treatment of Varicose Aneurysm Surg Clin North Amer, 11, 1029, October, 1931
- ¹¹ Holman, Emile. Arteriovenous Aneurysm The Macmillan Co, New York, 1937

DISCUSSION—DR JOHN HOMANS (Boston, Mass.) I shall address myself to the paper of Doctors Lee and Freeman. I have written out my discussion and I am sorry that I have done so, because the presentation with the pictures is so much more vivid and fascinating than I had anticipated from reading the paper alone.

The authors have called attention to the development of enlarged veins of a varicose type connecting with the malformed veins of the long cavernous hemangiomas of the limbs. I think this is not a very common combination, for I have seen four of these patients and only one of them suffered from this particular complication. That was a case which Dr Arthur W. Allen, of Boston, very kindly allowed me to see, and that patient, who may, for all I know, have suffered discomfort and even fainting when her veins were allowed to fill as soon as she got out of bed, wore, at all times, a very tight stocking and kept her veins compressed. It would be very interesting to know whether, if she had failed to take care of herself, she would have developed this same sort of difficulty which Doctors Lee and Freeman describe. In most cases which I have seen, the enlarged varicose vein has been an integral part of the angioma, without evident superficial venous connections, and has required no particular treatment except for its unsightliness. If, however, one attempts to deal with one of these vessels he will discover that there is a very important arterial communication of some sort, it may be by very fine arterial twigs between the surrounding tissues, which are very much scarred, and the great vein itself. On one occasion, I attempted to

remove one of these veins and the patient not only bled on the table but bled seriously on the succeeding days. The wound failed to heal and the patient, during the next few months, bled a great deal more. Finally, it was possible, by going to the apex of the lesion, to find the vessel at the point where it pierced the deep fascia. If I had been able, in the first place, to inject a radiopaque substance and had secured a venogram, I should have made the whole procedure easier, but in my case it was possible to determine where this opening was, and by incising the deep fascia I finally discovered the plexus of large veins beneath it with which this large varicose vein communicated. I was then able to do away with back pressure from that source and afterwards the use of sclerosing solutions obliterated practically all of the serious varicosity.

So I agree with Doctors Lee, Freeman and Reid that the best way to attack these conditions is to find the connection with either the superficial varicose veins or with the deeper vessels, and by abolishing that connection subsequent treatment is made very much easier.

For some reason, which I do not understand, the lesions of the upper extremities are much less common than those of the lower. I think de Takats has published several cases recently. These cases apparently require treatment only because the individual is likely to injure the large vessel or to injure the angioma, but, of course, they are unsightly. I should think some of these could be excised.

DR JAMES M. MASON (Birmingham, Ala.) World War No. 1 greatly stimulated interest in arteriovenous fistulae. As a result of the many wounds inflicted, there was a large amount of clinical material to be treated and studied. At this period, the fact was also established that cardiovascular disturbances resulted from the presence of these fistulae, and that these disturbances manifested themselves by local, peripheral, and central changes, some of which were not easy of explanation.

The immediate problem of the clinical surgeon was to give relief, if possible, by direct attack upon the local lesion, and to eliminate the fistulae. Various ingenious, and sometimes very difficult, operations have been devised for the accomplishment of this purpose.

It has been the problem of the cardiologist, the pathologist, and the experimental surgeon to investigate such phenomena as the blood pressure changes and bradycardiac phenomena observed on opening and closing a fistula, to explain the dilatation of the vessels proximal to the fistula, the hypertrophy and dilatation of the heart with decompensation and final congestive failure, and to account for the extensive collateral circulation which develops about the site of the fistula and makes quadruple ligation and excision of fistulae a safe operation in cases of long standing.

To the long list of contributors to the elucidation of these problems, Doctor Holman has added a brilliant piece of experimental work directed toward a better understanding of the most serious of these phenomena, namely, those that affect the blood volume, the arterial and vena-caval pressure and the degenerative changes in the heart.

In giving more careful study to his paper, and in comparing it with observations in certain of my clinical cases, I hope to arrive at an explanation of the question as to why patients with similar lesions react so differently in the matter of cardiac decompensation. Three of these have been reported (Mason, J. M. *ANNALS OF SURGERY*, 107, No. 6, 1029, June, 1938. *Idem Ibid.*, 109, No. 5, 735, May, 1939).

These fistulae resulted from gunshot and stab wounds in the subclavicular-axillary region: one on the right and two on the left side. The wounds

were approximately the same distance from the heart and were about the same diameter. One patient died from cardiac decompensation at the end of four days, without other injury or evidence of disease. Autopsy revealed a direct fistula with a wide lumen, between the subclavian vessels. The other two cases were under continuous observation of four and six months, respectively, before being operated upon. At no time did they show any evidence of cardiac embarrassment.

At operation which, in each instance, consisted of transvenous arteriorrhaphy, each case presented large varicosities in the region immediately adjacent to the fistula, indicating, to my mind, that obstruction to the free return of venous blood to the heart had taken place. In these two instances, hypertrophy may have kept pace with dilatation. The more likely explanation, however, is that the cause which resulted in production of the varicosities at the exact location of the fistula resulted in obstruction to the free return of blood to the heart, and thereby prevented its overfilling. In a previous communication, Holman has reported one case in which simple ligation of the vein proximal to the fistula resulted in obliteration of the thrill and caused the pulse to drop from 112 to 84. Harvey Stone reports a similar experience. Tixier and Ainulf have suggested that proximal venous ligation, some distance from the fistula, be employed in cases of great emergency, to relieve cardiac embarrassment until such a time as the patient may be able to undergo a curative operation.

DR MONT R. REID (Cincinnati, Ohio) Since Doctors Lee and Freeman have referred to two of my cases, I thought it might be interesting to give you a little more of the story of one whom I followed for 17 years. This patient came to me as a young girl, age 13, with an extensive angioma of the left leg, extending up to the crest of the ileum, involving the perineum and the left labium. Her complaints were fainting on assuming the erect position and having frequent attacks of hemarthrosis of the left knee. Her symptoms, at first, were largely relieved by the use of an elastic stocking. Later, we began a long series of treatments which included ligations of veins and injections of sclerosing solutions. To-day, at the age of 30, she is so much improved that, recently, she married and is soon to have a baby.

I simply cite this case to stress the importance of the fact that something can be done to relieve these patients. It often requires a great deal of patience and persistence to accomplish it, but in this case it has been most gratifying, even though it has taken 17 years to get what now appears to be a satisfactory result.

In connection with Doctor Holman's paper, I must say that what he has shown here to-day appears to be most convincing. We have not been able to completely confirm his blood volume studies and I do not know why. We see a great many cases of arteriovenous aneurysms in which we cannot demonstrate a marked, or any increase in the total blood volume. I grant that we see very few, in which the heart is badly damaged, in which there is not an increase in the total blood volume. However, everyone knows that in cardiac decompensation, cardiac failure, or impending cardiac failure, there is an increase in the total blood volume. Whether it is entirely proven by Doctor Holman that the changes in the heart are due entirely to the handling of an increased blood volume, or whether or not the increase in the blood volume may be in some way connected with a decrease in function of the heart, we do not know.

We recently had a case of arteriovenous aneurysm in a young man with an aortic insufficiency. He had a very large heart and a markedly increased

blood volume. We are not sure which condition caused the increased blood volume, and this observation has started us studying cases of aortic insufficiency to see if they have an increased total blood volume.

I should like to ask Doctor Holman if he has undertaken any acute, or nonsurvival experiments and measured the cardiac output immediately after opening the fistula between the aorta and the vena cava. So far as our studies are concerned, there is an enormous increase in cardiac output immediately after producing such a fistula, and on measuring the amount of blood returned to the heart through the inferior vena cava, there is a tremendous increase in the amount of blood going immediately back into the heart.

Doctor Holman's illustrations showing a reduction in the size of the heart for a few days after the production of a fistula appear to leave no grounds for any doubt as to this effect. However, in our sacrifice experiments, with the chest open, we got the impression that there occurred, in a very few minutes, a definite increase in the size of the heart, and all studies showed a very marked increase in the cardiac output immediately after producing such a fistula.

Of course, Doctor Holman and I have argued this question many, many times. He is probably right. I have never been able to agree with him that simply because there is an increased vascular bed there must of necessity be an increase of blood volume.

DR EMILE HOLMAN (San Francisco, Calif., closing). I should like to ask Doctor Reid what fills this increased vascular bed—air? Humor? There must be something to fill this enlarged vascular bed and it is blood. Doctors Dock and Harrison, at the Peter Bent Brigham Hospital, in 1923, showed a doubling of cardiac output the moment we introduced a fistula into the circulatory system, and that was shown not only the day after the introduction of the fistula, but it was shown months later with an increase in cardiac output during that time. There is no question about the increase in cardiac output the moment a fistula is introduced into the circulatory system.

Doctor Reid mentioned his acute experiments with the chest open. I do not believe they are comparable to experiments with the intact chest and the intact abdomen. Doctor Reid's experiments were also performed with a glass communication directly between the large vessels which did not permit bleeding into the distal venous bed, such as occurs in any arteriovenous fistula whether produced with a dagger, a bullet or by the experimentalist.

I also studied Doctor Reid's four clinical cases, in which he states that he did not get an increase in blood volume. A demonstrable increase in these cases would not be expected with present methods of determining blood volume. There was no increase in blood pressure or fall in pulse rate as I recall it, when he closed the fistula and there was very little dilatation of the heart. This suggests that the fistulae in these four cases were of small size. With ordinary methods of determining blood volume we cannot demonstrate increases in small fistulae. I do believe, however, that any fistula of any size causes an increase in blood volume and a dilatation of the heart and vessels but as our methods and instruments of precision are not sufficiently accurate, we cannot determine such small increases at the present time.

THE SURGICAL TREATMENT OF ANEURYSM OF THE ABDOMINAL AORTA^{*}

REVIEW OF THE LITERATURE AND REPORT OF TWO CASES,
ONE APPARENTLY SUCCESSFUL

I A BIGGER, M D

RICHMOND, VA

FROM THE DEPARTMENT OF SURGERY MEDICAL COLLEGE OF VIRGINIA, RICHMOND, VA

CLINICALLY recognizable aneurysms of the abdominal aorta occur infrequently, but the fact that Kampmeier¹ was able to collect 65 proven cases of aortic, and three cases of celiac aneurysm from the records of the Charity Hospital in New Orleans, over a period of 30 years, indicates that they are not extremely rare

The duration of abdominal aneurysms is difficult to determine, for they are deeply situated and are usually not suspected until they are far advanced. However, in 87.7 per cent of the 57 cases of Kampmeier's series, in which reliable data were available, symptoms had been noted for less than one year, and in 61.3 per cent of them, symptoms had been present for less than six months. Furthermore, death occurred within one month after admission to the hospital in 38 of the 68 cases. It is evident, therefore, that the disease is apt to run a rapidly fatal course.

Up to the present time, all forms of therapy have yielded poor results. Strictly conservative treatment offers little, and wiring, either with or without electrolysis, is at best only palliative. Judging from the literature, only a small number of surgeons have felt that direct surgical attack upon aneurysms of the abdominal aorta was justifiable, and it must be admitted that the results obtained by surgical intervention have been discouraging. However, a closer study of the reported cases reveals some cause for optimism. From 1817, when Sir Astley Cooper first ligated the abdominal aorta, to 1920, none of the 18 patients in whom the aorta (abdominal, 16, or lower thoracic, two) was occluded for abdominal aneurysm survived to leave the hospital. Since 1920, seven of the 12 patients in whom the aorta has been partially or completely obstructed for aneurysm have been discharged from the hospital as improved, and one other lived four and one-half months but did not leave the hospital (Table I). While it is not certain that any of these patients have been cured, the results demonstrate that occlusion of the aorta is not necessarily fatal. This information is important, for occlusion of the involved artery is necessary for the cure of most aneurysms. The only exceptions to this rule are found in those clearly sacculated aneurysms which may be treated by lateral ligation of the sac or by restorative aneurysmorrhaphy. Such

^{*} Presented by title before the American Surgical Association, St. Louis, Mo., May 1, 2, 3, 1940

TABLE I
LIGATIONS OF THE AORTA FOR ABDOMINAL ANEURYSM

PREVIOUS TO 1920

Surgeon	Year	Location of Aneurysm Sex and Age	Ligature Material	Level of Ligation	Survival Period	Cause of Death
1 Cooper ¹	1817	Left iliofemoral (male, 38 yrs)	?	Distal portion of aorta	3 days	?
2 James ²	1829	Left external iliac (male, 44 yrs)	?	Distal portion of aorta	3½ hrs	Shock
3 Murray ³	1834	Right iliofemoral (male, 33 yrs)	?	Distal portion of aorta	23 hrs	?
4 Montero ⁴	1842	Right iliofemoral (male, 30 yrs)	?	Distal portion of aorta	10 days	Hemorrhage
5 South ⁵	1856	Right common and external iliac (male, 28 yrs)	?	Distal portion of aorta	43 hrs	?
6 Stokes ⁶	1868	Right iliofemoral (male, 50 yrs)	Silver wire	Distal portion of aorta	12¾ hrs	Shock
7 McGuire ⁷	1868	Aorta and both common iliacs	?	Distal portion of aorta	Few hrs	?
8 Watson ⁸	1869	Iliac (male, 30 yrs)	?	Distal portion of aorta	65 hrs	Gangrene
9 Milton ⁹	1890	Aorta, ruptured (male, 45 yrs)	?	Distal to renal arteries	24 hrs	Shock and hemorrhage
10 Korte ¹⁰	1899	Right external iliac, rup- tured (male, 28 yrs)	?	Distal aorta (Sic opened 37 days after ligation of common iliac Severe hem- orrhage Aorta ligated)	1 hr	Shock and hemorrhage
11 Keen ¹¹	1899	Proximal abdominal aorta, ruptured	?	Below diaphragm	48 days	Cutting through of ligature
12 Tillaux ¹²	1900	Left iliac, ruptured (male, 52 yrs)	?	Terminal aorta	39 hrs	?
13 Morris ¹³	1901	Midportion of abdominal aorta (female, 24 yrs)	Soft rubber cath- eter and clamp forceps	Terminal aorta	?	Gangrene of bowel from pressure by forceps
14 Halsted ¹⁴	1906	Extending from above in- ferior mesenteric artery to near diaphragm (male, 36 yrs)	Aluminum band	Band applied to aorta below inferior mesenteric 23 days after one had been applied to thoracic aorta	18 days	Rupture of aneurysm

15	Halsted ¹⁶	1908	Left common iliac (male, 58 yrs)	Tape, after rupture of aorta while attempt was being made to apply aluminum band	Terminal aorta	12 hrs	Hemorrhage and shock in patient with hypertrophied and dilated heart
16	Halsted ¹⁵	1909	Aorta, extending from renal arteries to bifurcation (male, 53 yrs)	Aluminum band	Between renal and superior mesenteric branches (Partial occlusion)	47 days	Abscess developed at site of band Death from results of infection
17	Halsted ¹⁷	1911	Aorta, below renal arteries (elderly woman)	Aluminum band	Below renals	6 wks	Hemorrhage from cutting through of band
18	Heuer ¹⁸	1917	Abdominal aorta at level of celiac axis (male, 31 yrs)	Aluminum band	Lower thoracic aorta (Partial occlusion)	1 mo , 9 days	Rupture of aorta at site of band
SUBSEQUENT TO 1920							
19	* Vaughan ¹⁹	1920	About origin of superior mesenteric artery (male, 39 yrs)	Cotton tape (1/2 inch)	Distal to aneurysm below inferior mesenteric artery (Partial occlusion)	2 yrs , 1 mo	? (Aneurysm much larger but had not ruptured)
20	Reid ²⁰	1921	About level of inferior mesenteric artery (male, 36 yrs)	Cotton tape	Proximal to celiac artery (Previously partly occluded between inferior mesenteric and renal arteries)	4 1/2 mos (after first operation)	Rupture of aneurysm
21	Watts ²¹	1923 (Feb 26)	From superior mesenteric artery to near bifurcation (female, 28 yrs)	Cotton tape	Just above superior mesenteric artery	22 hrs	Renal arteries came off of sac Patient developed suppression of urine Ligature was loosened about 3 hrs before death but pulsation did not return to sac
22	* Matas ²²	1923 (Apr 9)	Terminal aorta (female, 28 yrs)	Cotton tape	Below inferior mesenteric artery	1 yr , 5 mos	Massive, tuberculous, pulmonary hemorrhage (Aneurysmal sac almost obliterated)
23	* Watts ²¹	1923 (Sept 15)	Below superior mesenteric, extending almost to bifurcation (female, 60 yrs)	Cotton tape	Below superior mesenteric artery (Partial occlusion)	3 1/2 yrs	Rupture of aneurysm (?) No autopsy
24	* Brooks ²³	1925	Terminal aorta (male, 59 yrs)	Fascia lata (proximal) and heavy silk (distal to fascia)	Distal to inferior mesenteric artery	About 3 mos	Intestinal obstruction (Aneurysmal sac obliterated)

TABLE I (Continued)

Surgeon	Year	Location of Aneurysm Sex and Age	Ligature Material	Level of Ligation	Survival Period	Cause of Death
25 Reid ²⁴	1928	Aorta at level of celiac axis (female, 35 yrs)	Insertion of fascial plug with fixation by silk sutures	Lower thoracic aorta	12 hrs	Hemorrhage from divided intercostal artery
26 Andrus ²⁵	1929	Lower epigastric region (male, 57 yrs)	Cotton tape	Artery doubly ligated and divided between tapes in lower thoracic region	1½ hrs	Shock
27 * LaRoque ²⁶	1929	Right common iliac (female, 30 yrs)	Umbilical tape and heavy silk	Distal abdominal aorta (Subtotal occlusion)	?	Alive and greatly improved at end of 14 mos
28 Bigger	1938	From inferior mesenteric to bifurcation of aorta (male, 54 yrs)	Fascia lata	Proximal to inferior mesen- teric artery	18 hrs	Left-sided heart failure Pulmonary edema
29 * Bigger	1938	Level of inferior mesenteric (male, 25 yrs)	Fascia lata	Proximal to inferior mesen- teric artery Endo aneu- rysmorrhaphy 1 mo later		Alive and apparently well
30 * Elkin ²⁸	1939	Terminal aorta (male, 50 (?) yrs)	Cotton tape	Distal to inferior mesenteric artery (Subtotal occlu- sion)		Alive and at work, 11 mos later

* Successful case

aneurysms are not common in any location and are particularly rare in connection with the abdominal aorta

If the foregoing statements are true, the following problems need to be clarified (1) Under what circumstances may the aorta be occluded with reasonable chance of success, (2) what method of occlusion is preferable, and (3) is proximal occlusion curative? If not, is the Matas operation (obliterative endo-aneurysmorrhaphy) feasible in spontaneous aortic aneurysm? None of these questions can, as yet, be answered with any assurance but some important evidence bearing on them should be given consideration

In regard to the circumstances under which aortic occlusion may be considered justifiable, it seems obvious that in elderly or greatly debilitated patients the chances of success are diminished and it is doubtful if such an operation should be undertaken on very poor-risk patients. If operation is undertaken, it is almost certain that the occlusion should be accomplished in more than one stage. Extensive, diffuse calcification of the aorta should probably be considered a contraindication to surgery

The portion of the aorta involved and the importance of the branches arising from the aneurysmal sac have an important bearing on the prognosis. For example—it is reasonable to suppose that aneurysms arising from the aorta distal to the renal arteries will be more susceptible to surgical cure than those arising proximal to these vessels. This would appear likely because the effect on the circulatory apparatus is less pronounced the farther the lesion is from the heart, and, more important still, because there is danger of occlusion of essential arteries such as the superior mesenteric, the celiac, or the renals when the proximal portion of the abdominal aorta is involved. It has been shown by Halsted and Reid that the aorta may be occluded above the renal arteries, but if that portion of the aortic wall from which the superior mesenteric, the celiac, or the renal arteries arise is involved in the aneurysmal sac, ligation of the aorta will, almost certainly, result in occlusion of the origin of these essential vessels by clot and, thus, will result in an insufficient circulation to the organs supplied by them. Stated in a different way, the collateral circulation may be sufficient to nourish the stomach, intestines, and kidneys when the aorta is obstructed proximal to the origin of the celiac, superior mesenteric, or renal arteries, but only through the lumen of the aorta distal to the obstruction. It is, therefore, probably wiser to discontinue an operation when any of these vessels is found to arise from the wall of the aneurysmal sac. This apparently does not apply to the inferior mesenteric artery, for, as demonstrated by Archibald,²⁹ the main trunk of this artery may be occluded without producing necrosis of that portion of the intestine supplied by it.

A study of the results of occlusion of the aorta by the various materials now in use convinces one that none of them is satisfactory and there is no unanimity of opinion as to which one is best. Most of the reported failures may be attributed to one or the other of the following causes. (1) Either the ligatures rapidly cut through the wall of the aorta and cause fatal hemorrhage,

or (2) they fail to produce a permanent occlusion of that vessel. Fascia has many advantages for temporary or preliminary partial occlusion, but the results are not permanent. Matas recommends cotton tape, and it is probably significant that it was the material used in four of the seven more or less successful cases so far reported, but even wide tape may cut through the aortic wall and probably always gives, to some extent, after a few days.

In all except a few cases of aneurysm of the abdominal aorta which have been operated upon, the surgical procedure has been limited to an attempt to occlude the aorta, usually proximal to the origin of the sac. Proximal occlusion of the aorta is undoubtedly an essential part of the operative procedure in most cases, either preliminary to, or as a part of some more extensive operation, but there is considerable reason to doubt that proximal ligation alone will cure an appreciable number of cases even if the occlusion can be made complete and permanent. It is known that occasionally an aneurysmal sac spontaneously becomes filled with clot and is obliterated. This naturally occurs in a certain percentage of cases following proximal occlusion, and Halsted,¹⁷ Matas,¹⁰ Reid¹¹ and Holman¹² have obtained such results in iliac and femoral aneurysms, but it does not seem reasonable to suppose that it will happen frequently. Brooks²³ obtained complete obliteration of an aneurysm of the terminal aorta following proximal occlusion of that vessel but points out that this result probably occurred because the common iliac arteries were largely obstructed by pressure from the aneurysmal sac. The condition was, therefore, essentially similar to that produced by proximal and distal ligation. If there is a sufficient collateral blood flow to nourish the tissue distal to the obstruction, there is apt to be sufficient reflux flow to prevent complete and permanent obliteration of the aneurysmal sac. It would seem, therefore, that proximal occlusion of the aorta should be undertaken as a preliminary to more extensive procedures in suitable cases. In cases not suitable for other procedures, proximal occlusion may be valuable for palliation.

In carefully selected cases of abdominal aortic aneurysm, it would seem wise to perform a preliminary partial or subtotal proximal occlusion of the aorta, then, after a suitable delay, perform aneurysmorrhaphy or possibly aneurysmectomy. Unfortunately, it is probable that few cases are suitable for either of these procedures. Thus far, they have been attempted in only a small number of cases, some of which were obviously not suitable.

Bogoraz²³ reported a case which he described as an arteriovenous aneurysm between the abdominal aorta and the left renal vein. The aneurysmal sac, which was about the size of a goose egg, arose at the site of origin of the left renal artery from the aorta. A proximal ligature was applied between the sac and the aorta and a distal ligature was then applied to the renal artery, and the sac excised. The kidney was also removed. The patient recovered. Although this is described as an aortic aneurysm, the fact that he was able to ligate the neck of the sac makes it appear likely that it originated from the

base of the left renal artery which may have been greatly dilated as a result of the fistula

Brooks³⁴ attempted excision of a large thin-walled aneurysm of the terminal aorta but this had to be abandoned because of rupture of the sac followed by excessive hemorrhage. The aorta was then ligated proximal to the aneurysm and, as was previously pointed out, this resulted in complete obliteration of the sac. So far as can be determined, there has not been a successful excision of a true aortic aneurysm.

Aneurysmorrhaphy for the cure of aneurysm of the abdominal aorta has been attempted by Lozano,³⁵ Munro,³⁶ Crile,³⁷ Kummel³⁸ and Biggert (traumatic). All of the patients so operated upon, except the one reported in this paper, died. A report of Crile's case has not been available for study, but a review of Munro's, Kummel's, and Lozano's reports brings out certain points in the technic employed in each of these operations which may be significant in relation to the outcome.

Munro did not provide for occlusion of the aorta either proximal or distal to the aneurysm, so when the thin sac was torn while it was being fixed up he had to control hemorrhage by applying a stomach clamp tangentially. He then attempted to obliterate the sac by suture while the clamp was in place. This was naturally less satisfactory than a more deliberately executed intiasaccular suture of the vascular openings. Munro's patient died from hemorrhage the night following operation.

Kummel approached an aneurysm of the proximal portion of the abdominal aorta through the chest wall and diaphragm. The aorta was compressed proximally but not distally when the sac was split open. Apparently, the intiasaccular suture was reasonably satisfactory but after the repair had been completed a gauze tampon was inserted between the aorta and spine. This caused bleeding which was difficult to control and Kummel blamed his failure on this maneuver. However, it is probable that there was considerable unnecessary hemorrhage from the distal aorta during the primary suture and that this played an important part in the unfortunate outcome in this case.

Lozano applied clamps (without rubber coverings) to the very sclerotic aorta above and below the aneurysm before opening the sac. He then closed the arterial openings in the sac by suture and obliterated it. This part of the operation was apparently successfully accomplished, but when the obstructing clamps were removed there was bleeding where the sclerotic vessel wall had given way beneath them. It is possible that, with such advanced sclerosis, any form of compression would have produced the same result, but unprotected clamps would be particularly likely to cut through such a vessel wall.

Careful provision for the control of hemorrhage is essential in either excision or intiasaccular suture of aneurysm. In peripheral aneurysms this is best accomplished by the use of a tourniquet but when large arteries of the trunk are involved the main vessel must be occluded both proximally and distally and, in addition to this, collateral vessels entering the sac should be

ligated when possible before the sac is opened. If these precautions are not taken, excessive hemorrhage is apt to occur.

There are many unsolved problems in connection with the surgical treatment of aneurysms of the abdominal aorta. Some of them may be solved by carefully controlled animal experiments, but others can be solved only by observations on patients with aortic aneurysms. For this reason it is essential that such patients, especially those subjected to operation, be carefully observed and that the results be reported in detail.

With this in mind, the author presents the following two cases.

CASE REPORTS

Case 1—R. E. C., white, male, age 54, was admitted to the Memorial Hospital, Richmond, Va., February 11, 1938, complaining of a pulsating mass in the abdomen and pain in the right hip. He had noticed the abdominal pulsation about eight months before but the pain in the right hip was of only three weeks' duration. His past history was not significant.

Physical Examination—The patient was a frail, moderately emaciated white male who appeared to be about 60 years of age. He was inclined to remain in the dorsal recumbent position with the right thigh flexed on the abdomen at an angle of approximately 90°. The abdomen and lower extremities presented the only significant findings. Abdominal examination revealed a firm, pulsating mass extending across it at about the level of the umbilicus, more prominent to the left of the midline. There was also a sausage-shaped mass in the right lower quadrant which was quite tender. There was atrophy of the muscles of both legs. No edema.

His temperature fluctuated between 99° and 101° F. Blood pressure 100/50. RBC 2,880,000, Hb 60 per cent, WBC 12,500, 78 per cent polymorphonuclear neutrophils. Wassermann negative. Blood sugar 91, nonprotein nitrogen 34. Urine negative. *Clinical Diagnosis*—Aneurysm of the abdominal aorta.

The moderate elevation of temperature, leukocytosis, and increasing pain were erroneously interpreted as being due to a retroperitoneal rupture of the aneurysm, so it seemed wise to obstruct the aorta proximal to the aneurysm.

Operation—February 21, 1938. Under general anesthesia, the right thigh could be easily extended, indicating that its flexion had been due to spasm of the iliopsoas muscle. The abdomen was entered through a right paramedian incision extending from the mid-epigastrium to the pubis. It was found that the aneurysm extended considerably above the most prominent, externally palpable portion of the sac, arising about 2 cm. below the third portion of the duodenum at the origin of the inferior mesenteric artery. The second aneurysm involved the right iliac artery, and a poorly defined mass extended laterally and upward beneath the terminal ileum and cecum. The posterior peritoneum was carefully incised just proximal to the aneurysm. The root of the mesentery was separated up for a short distance and retracted to the right, thus exposing the third portion of the duodenum which was retracted upward, to expose the aorta. An aneurysm needle was passed around the aorta just above the aneurysm and a strand of chromic catgut drawn around the vessel. A segment of fascia lata, about five inches in length and about 1 cm. in width, was removed from the right thigh, attached to the catgut ligature, and pulled around the aorta. The strip of fascia was then tied down sufficiently tightly to cause complete disappearance of all pulsations distal to it and the knot fixed by a heavy silk suture-ligature. A doubled, heavy silk ligature was left around the aorta for future identification. It was not tied. The vena cava was not occluded.

Blood pressure was 95/60 when the operation was started and remained remarkably constant throughout the procedure, showing no change when the aorta was occluded. When he was returned to the ward from the operating room his blood pressure was

90/50 and it remained at approximately this level for ten hours. It then began to fluctuate and the systolic pressure ranged between 120 and 60.

Postoperative Course—Immediately following operation, both feet and legs were warm but the right foot was somewhat paler than the left. About six hours after operation, the right foot and leg became pale and cold, but the color and temperature of the left one remained good, and a faint pulse was palpable in the left femoral artery. The right femoral artery remained pulseless, and, at the end of 12 hours, the right leg was becoming shriveled in appearance and showed areas of discoloration over the dependent portions. It seemed obvious, at this time, that the circulation in the right leg was inadequate, therefore, the right femoral vein was ligated, with the hope that this might improve the circulatory balance in that leg.

Twelve hours after the first operation, his systolic blood pressure fell to 60, and 500 cc of whole blood was administered. His pressure rose to 104 but two hours later dropped to 90, and remained at that level until an hour before his death. He developed edema of the lungs and died 18 hours after ligation of the aorta.

Autopsy—An aneurysm of the distal portion of the abdominal aorta and another of the right common iliac artery were found, both apparently due to arteriosclerosis. The ill-defined mass in the right side of the abdomen was a large retroperitoneal abscess. He also had generalized arteriosclerosis, chronic interstitial nephritis, occlusion of the right ureter with pyelonephritis and associated venous thrombosis, a large soft spleen, and other signs of severe sepsis. The immediate cause of death was left-sided heart failure with pulmonary edema. When the aorta was opened the site of occlusion was found to be sufficiently patent to permit the passage of an ordinary probe, but the aneurysmal sac was largely filled by fresh clot. The distal portion of the iliac aneurysm was filled by old clot and its proximal portion by fresh clot. The lumen of the external iliac artery was occluded by advanced arteriosclerotic changes and a fresh thrombus filled the internal iliac (hypogastric) artery.

Comment—Since the autopsy showed long-standing occlusion of the external iliac artery, the acute circulatory deficiency following aortic occlusion is adequately explained by the formation of a clot in the hypogastric artery and its major branches, for, under the circumstances, this vessel was an essential collateral channel. Failure of the left side of the heart probably resulted from the additional burden imposed upon a cardiac musculature greatly weakened by prolonged sepsis. Occlusion of the aorta, *per se*, probably played an unimportant part in the outcome, and abdominal exploration without aortic occlusion might well have led to the same result.

Case 2—C. C., white, male, age 25, was admitted to the Memorial Hospital, December 13, 1938, at 3 30 o'clock P. M., and stated that he had felt well the previous day but at about 6 00 o'clock A. M., on the day of his admission, he leaned over to wash his face, became dizzy, and fainted. After he regained consciousness he had severe abdominal pain, most marked in the midepigastrium and radiating to the region of the left shoulder blade. He vomited once and had a bowel movement, but the severe pain persisted. When first examined by a physician he was pulseless and complained of extreme thirst.

Physical Examination—Temperature 101° F, pulse 140, respirations 22, blood pressure 50/30. He was very pale. There was no cyanosis and no distention of the neck veins. Heart rate was rapid, rhythm regular, no murmurs. His pupils were constricted. The abdomen was rigid and apparently contained fluid. *Tentative Diagnosis* Ruptured abdominal aortic aneurysm. This was considered especially likely because of the following history.

On September 7, 1937, this patient was admitted to the Galax Hospital, Galax, Va., for the treatment of multiple buckshot wounds. One shot had entered below the crest of

the right ilium and had coursed completely across the body and was lying in the left side near the anterior end of the eleventh rib. The patient was badly shocked and presented the signs of intra-abdominal injury. At operation no intestinal perforation was found but there was a massive retroperitoneal hemorrhage, the origin of which was not determined. He was discharged from the hospital 14 days later, and had apparently been in good general health until the onset of the present trouble.

A short time after admission to the Memorial Hospital he was given 450 cc of blood by the multiple syringe method, following which his condition showed marked improvement. At 8 00 o'clock P M, four and one-half hours after his admission, his blood pressure was 130/82, pulse 112, temperature 101.6° F. Although his abdomen was rigid and distended, it was thought that a pulsating mass could be felt about one inch to the left of the umbilicus. Pulsation in the vessels of the lower extremities was full and equal.

Before transfusion his blood showed R B C 3,280,000, Hb 58 per cent, W B C 30,000, 92 per cent polymorphonuclear neutrophils, Wassermann and Kline reactions negative. The following morning his blood findings were R B C 2,900,000, Hb 44 per cent, W B C 21,500, 92 per cent polymorphonuclear neutrophils. His urine was negative.

At 8 30 o'clock on the morning after admission his blood pressure was still normal and his pulse of good volume. At 8 45 o'clock, 15 minutes later, he had another attack of syncope and his pulse and blood pressure could not be obtained. The foot of his bed was elevated and he was given 600 cc of blood by the multiple syringe method. After this attack of syncope his abdomen became greatly distended and there was definite evidence of free fluid in the peritoneal cavity. The patient complained of very severe, continuous abdominal pain. Exploration of the abdomen in an attempt to control the bleeding was decided upon.

Operation—At 4 00 o'clock P M the patient was given 150 mg of novocain intraspinally. At the time of the intraspinal injection his blood pressure was 110/70, but it dropped rapidly and when the abdomen was opened his systolic pressure was only 70 Mm Hg. Shortly thereafter it was impossible to determine it. The old left rectus scar, the result of his operation 15 months previously, was excised and the incision lengthened both above and below so that when completed, it extended from about two inches below the left costal margin to about two inches above the pubis. A massive intra-abdominal hemorrhage, partly clot and partly liquid blood, was found. About 500 cc of this blood was removed, citrated, filtered, and administered intravenously. In addition to this, he was given 500 cc of blood from a donor, the entire liter of blood being administered during the course of the operation. The bleeding had come from the rupture of an aneurysm of the lower portion of the abdominal aorta but there was no bleeding when the abdomen was opened, as the tear in the anterior wall of the aneurysm was plugged by a firm clot. Although the bleeding had temporarily stopped, it was felt that the aorta must be obstructed proximal to the aneurysm to prevent a recurrence of the hemorrhage. The aneurysm, which was about 8 to 10 cm in diameter, arose from the anterior wall of the abdominal aorta at the level of the inferior mesenteric artery.

An incision was made through the posterior peritoneum immediately above the aneurysm, and the third portion of the duodenum was exposed, freed up, and retracted upward to expose the aorta (Fig 1). The aorta was separated from the vena cava, and an aneurysm needle carrying a heavy catgut ligature was carefully passed around the artery, three heavy catgut ligatures were then tied to the first one and drawn around the vessel. A strip of fascia lata about three-quarters of an inch wide and six to eight inches long was removed from the left thigh, attached to one of the catgut ligatures, and drawn around the aorta twice. It was tightened until all distal pulsation ceased, and fixed by silk sutures. A long piece of heavy silk was left in place around the aorta for future use. Before the aorta was occluded a pronounced, continuous thrill could be felt in one of the adjacent vessels. This thrill could not be felt after the aorta was occluded, so its site was never definitely determined, but it was thought that it was an arteriovenous fistula, probably involving the mesenteric vessels.

Immediately following occlusion of the aorta the systolic blood pressure rose sharply to 180 Mm Hg, and the patient had a mild convulsive seizure. Two hours after his return to the ward he was able to move his arms and legs. His feet and lower legs were cold, pale, and the veins were collapsed, but the upper legs and thighs were warm and of good color.

Postoperative Course—The following morning (December 15) his general condition was satisfactory, systolic blood pressure 140, lower extremities were warm, and the color

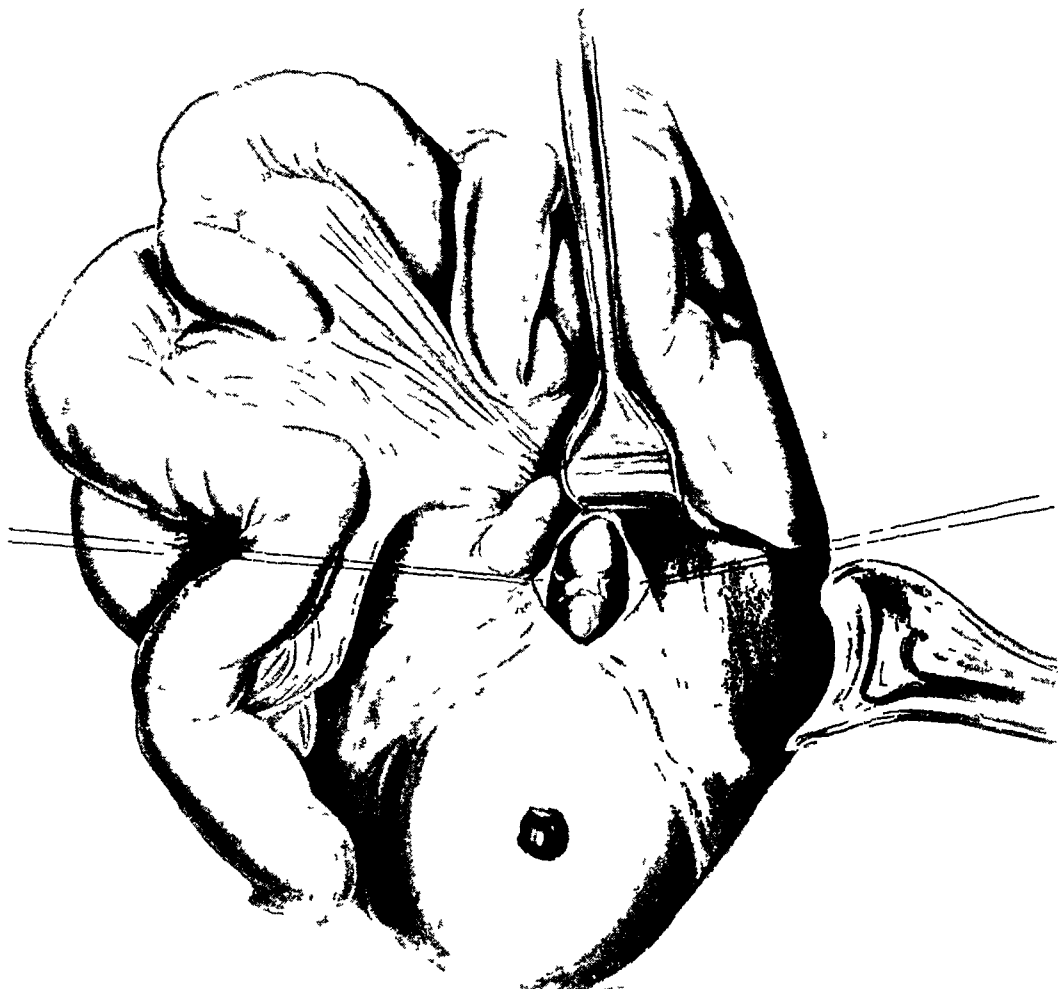


FIG 1—Case 2 Drawing showing point of rupture of aneurysm and level of occlusion of the aorta

of his feet was much improved, but no pulsations could be made out in any of the arteries of the lower extremities, including the femorals. It was discovered, however, that during the night the patient had developed complete paralysis of both lower extremities. There was also marked diminution in tactile sensation and widespread involuntary muscular twitching. These findings suggested involvement of the nerves as a result of marked temporary anemia.

Saline absorption by Dr. Nathan Bloom on December 15, the day after operation, was as follows:

	Right Leg	Left Leg
Inner side of foot	20 minutes	15 minutes
Inner side of midportion of lower leg	30 minutes	25 minutes
Patella	30 minutes	25 minutes
Midthigh	30 minutes	—

On December 16, he complained of numbness and tingling of his lower extremities but was still unable to move them.

On December 17, sensation had not returned to the lower legs but he was able to flex his knees slightly.

On December 20, he began to complain of burning and aching in his legs, and for several days this was so severe as to require opiates for its relief. He was unable to void until the fourth postoperative day.

Neurologic examination by Dr. Gayle Crutchfield, December 22, showed that all of the deep reflexes of the lower extremities were abolished except the right prepatellar, which was hypo-active. Plantar response was normal. All muscle groups showed greatly diminished power. In addition to the above findings there was hypesthesia below both knees, extending down to and including a part of the dorsum of each foot. His impression was that the neurologic changes were the result of temporary anemia of the peripheral nerves of the lower extremities.

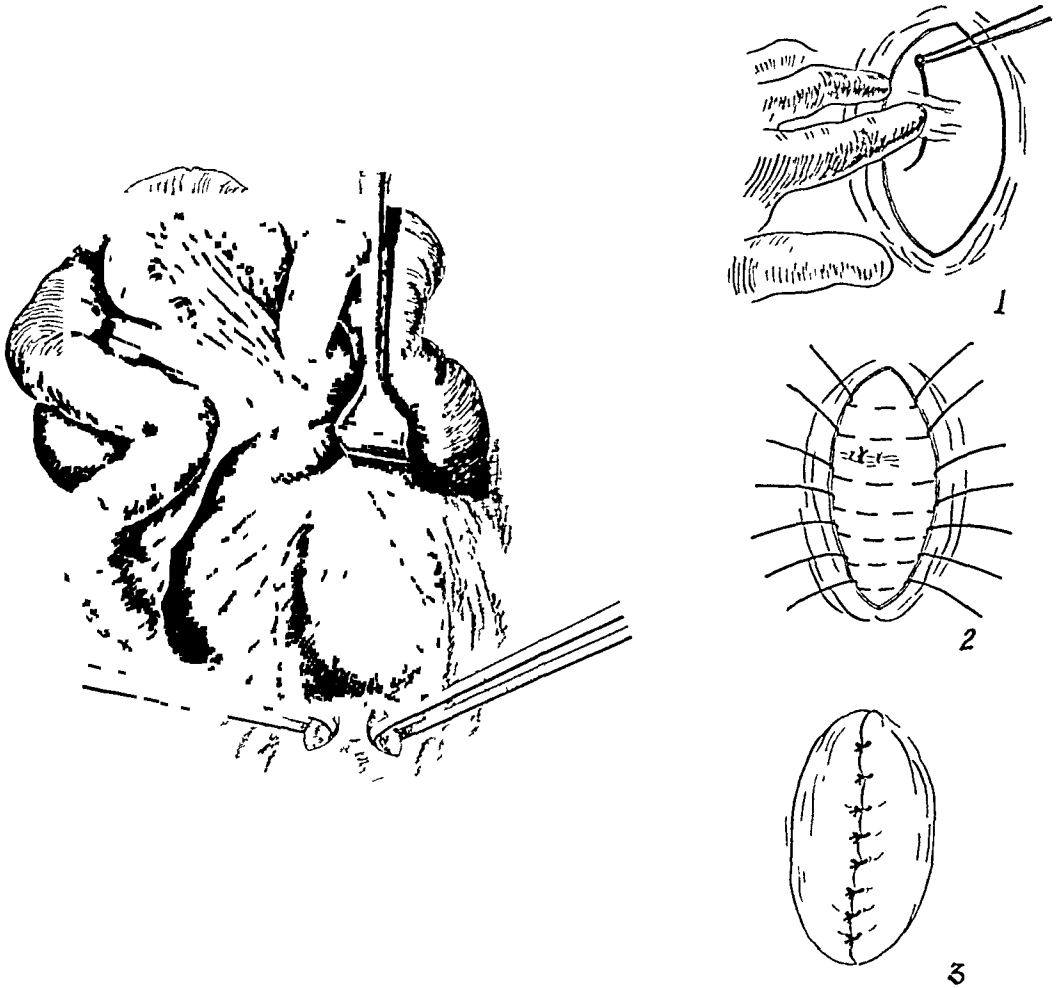


FIG 2—Case 2. Drawing showing the reduction in the size of the aneurysm one month after the occlusion of the aorta. (1) The method of occluding the opening between the aorta and aneurysmal sac. (2 and 3) Obliteration of the aneurysmal sac.

On December 23, the patient was able to move his feet and toes, and was conscious of the sense of pressure, but the finer senses of touch and slight pain had not returned. Muscular twitching had completely disappeared.

On January 4, 1939, pulsation was detected on both sides just above the inguinal ligaments. This was thought to be in the deep epigastric arteries, as no pulsation could be made out below the inguinal ligaments. Sensation and motion were both greatly improved, but he still complained of pain in the thighs, knees, and ankles.

Second Operation—On January 10, the patient was again operated upon. Under general anesthesia, the left rectus scar was again excised with especial care to avoid injury to the left deep epigastric artery, an important collateral vessel. The omentum

was adherent to the parietal peritoneum but the bowel was free. The aneurysmal sac was reduced to about one-half its previous size and was not pulsating. The iliac arteries were not pulsating. A loop of small bowel adherent to the area at which the sac had ruptured was freed up without particular difficulty. The heavy silk ligature which had been placed around the aorta proximal to the aneurysm was found and preserved so that it could be used to control bleeding from above. Both common iliac arteries were exposed and heavy silk ligatures placed around them for the control of retrograde hemorrhage (Fig 2). After these provisions had been made for the control of bleeding, the aneurysmal sac was opened in a perpendicular direction and several pieces of tissue were removed from its wall for microscopic study.

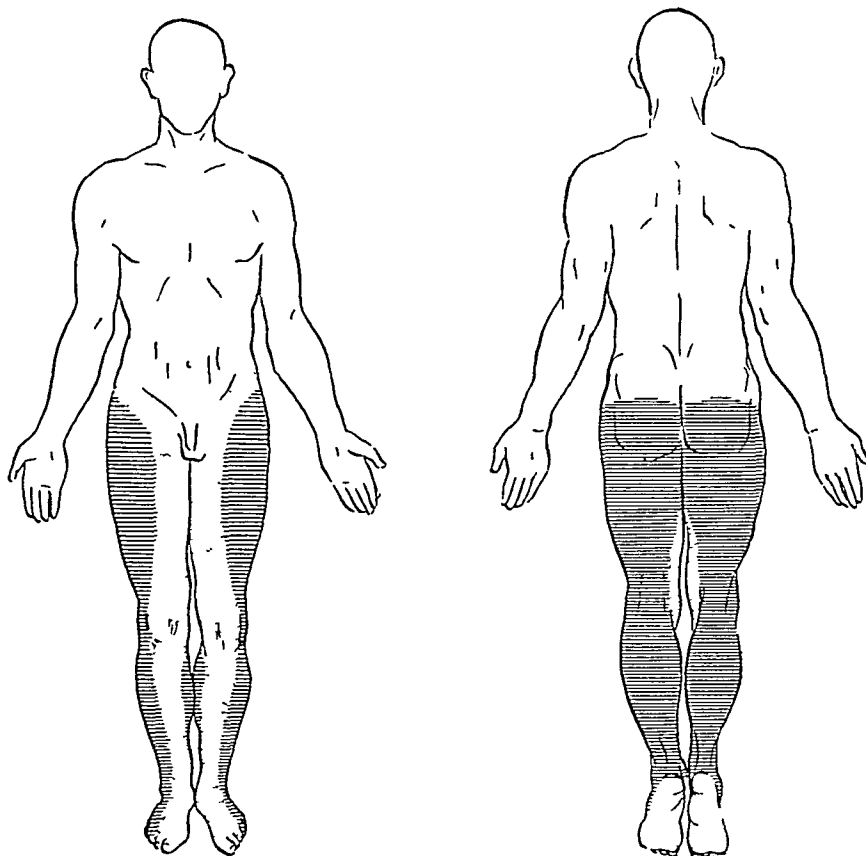


FIG. 3—Case 2. Sensory changes following occlusion of the abdominal aorta. The dotted areas indicate slight hypesthesia to pain and temperature. The transverse lines indicate the areas of marked hypesthesia to pain and temperature.

Pathologic Examination—Dr. George Z. Williams: "The specimen submitted for examination consists of several small pieces of dense, pink tissue measuring about 2.5 cm in greatest length and obviously from the wall of some type of sac.

Microscopic Examination—The paraffin imbedded and hematoxylin-eosin stained sections taken from this material reveal the characteristic structures of arterial wall. However, there is marked degenerative change with much necrobiosis in which the fibers of elastic tissue can still be identified but distortion caused by sclerosis and collagenous increase is marked. There is no sharp demarcation between the degenerating sclerotic arterial walls and the superimposed hyalinized platelet thrombus which also shows degenerative changes. Infiltration of chronic inflammatory cells, particularly monocytes, around small patches of hemorrhage is seen in various portions of the arterial wall. Some evidence of old hemorrhage is seen in the presence of cells containing hemosiderin pigment and these are scattered through the fibroblastic sclerotic areas. No specific inflammatory changes can be seen. These changes are typical of a severe sclerotic lesion of the arterial wall with old and recent hemorrhages in the wall which are undergoing healing changes."

A considerable quantity of blood clot was removed from the sac without encounter-

ing hemorrhage, but when a dense piece of clot was removed from the upper right posterior wall of the sac, overlying the anterior portion of the aorta, bright red blood came out under considerable pressure. It was possible to control this by placing the distal phalanx of the left index finger in the communicating opening. A silk suture was passed deeply through the lower edge of the opening beneath the finger, then out through the upper edge. Large bites of tissue were included on both sides of the opening and when tension was made on this suture it was found that bleeding was largely controlled. When additional sutures were placed on each side of it there was no further bleeding even when the silk loops around the aorta and the common iliac arteries were released. The aneurysmal sac was obliterated by six silk sutures passed from the left, through the posterior wall of the sac and then through the upper right side of the sac. The margins of the sac were approximated with interrupted sutures of silk and the omentum was tacked over the suture line.

At this second operation it was found that the lower sigmoid and rectum were firmly adherent to the walls of the pelvis, possibly due to circulatory changes in the bowel following occlusion of the aorta.

At the completion of the operation the patient's general condition was good. Systolic blood pressure 130, pulse 114.

Subsequent Course—On January 17 Dr Gayle Crutchfield noted little change in the neurologic picture. The right prepatellar reflex was somewhat more active but he was still unable to elicit other deep reflexes in the lower extremities.

Oscillometer readings by Dr Nathan Bloom, January 22, were as follows:

	Right Leg	Left Leg
Midthigh	0.5 to 1 unit	0.5 to 1 unit

and on February 10, were

Midthigh	1.5 to 2 units	1.5 units
----------	----------------	-----------

He was discharged from the hospital February 14, 1939, two months after admission. His weight, normally, was about 165 pounds but at this time it was only 137 pounds.

On May 25, 1939 his weight was 160 pounds and his general condition was excellent. Blood pressure 138/85. Heart sounds were normal in character, and the heart was not enlarged. No mass could be felt in the region of the aneurysmal sac. There were neither motor nor sensory disturbances in the extremities. Reflexes were normal. There were pulsations in the femoral, popliteal, and posterior tibial arteries but none could be made out in the dorsalis pedis arteries.

Oscillometer readings by Dr Nathan Bloom, May 25, 1939, were as follows:

	Right Arm (at pressure of 100 Mm Hg) 5 units	
	Right Leg (at pressure of 90 Mm Hg)	Left Leg (at pressure of 90 Mm Hg)
Midthigh	3.5 units	4.0 units
Below knee	4.0 units	3.5 units
Ankle	2.0 units	2.5 units

The patient was seen again, January 30, 1940. His weight was 165 pounds. He stated that his feet became cold a little more noticeably than they had previously but otherwise he had no trouble in his lower extremities. Abdominal examination showed the incision firmly healed, with no evidence of hernia. The abdomen was flat and easily palpated. A bruit could be made out just to the right of the umbilicus and one and one-half inches above it. The bruit was more pronounced during systole but appeared to be continuous in character, suggesting an arteriovenous fistula. In other words, it was of the same character as at the time of the first operation, before the aorta was occluded, and was more distinct than in May, 1939. This suggested an arteriovenous fistula between some of the vessels arising below the aortic occlusion, probably the inferior mesenteric

artery and vein Blood pressure in the left arm was 120/60, and in the left thigh 125/80

A teleroentgenogram of the chest showed the transverse diameter of the great vessels to be 47 cm, of the heart 10.9 cm, of the thorax 26.4 cm, a cardiothoracic ratio of 41 per cent. The lungs were clear. The domes of the diaphragm were normal. Anteroposterior and lateral roentgenograms of the lower dorsal and lumbar vertebrae and sacrum showed no erosion of the vertebral bodies. The psoas muscles were well outlined and no evidence of an aneurysmal mass could be made out in any view.

Comment—Fascia was used to occlude the aorta at the first operation because only temporary occlusion seemed indicated. The heavy silk ligature was left around the aorta to occlude it during the aneurysmorrhaphy in case the strip of fascia no longer produced subtotal occlusion. The iliac arteries were exposed and heavy ligatures (tapes would have been better) passed around them for the control of retrograde bleeding when the sac was opened. In spite of these precautions there was considerable pressure in the aorta presumably from the lumbar and middle sacral arteries which entered the aorta below the point of occlusion.

It is believed that the strip of fascia has now completely disappeared and that the lumen of the aorta is fully restored. There is no evidence of recurrence of the aneurysm.

SUMMARY

An attempt has been made to collect the cases of aneurysm of the abdominal aorta and common iliac arteries treated by operations (excluding wiring) upon the aorta. The various surgical procedures which may be applicable to these aneurysms (excluding wiring) are discussed.

Two new cases are reported.

Case 1, a poor surgical risk, developed left-sided heart failure with pulmonary edema and died following occlusion of the aorta proximal to the aneurysm.

Case 2, a young man with a ruptured traumatic aneurysm, had a preliminary occlusion of the aorta proximal to the aneurysm and one month later a restorative endo-aneurysmorrhaphy. When examined one year after the endo-aneurysmorrhaphy, the patient appeared to be well, there was no evidence of aneurysm and the lumen of the aorta was obviously patent.

We realize that there is a marked difference between traumatic and spontaneous aneurysms and that the methods of treatment used in one may not be applicable in the other. For example, it is unlikely that one would find a spontaneous aortic aneurysm suitable for the type of operation, reconstructive endo-aneurysmorrhaphy, used in our second case but it seems likely that a small number of spontaneous aneurysms will be found suitable for obliterative endo-aneurysmorrhaphy. Such operations probably should not be attempted unless the aneurysm arises distal to the renal arteries and, almost certainly, should not be attempted when the aorta is diffusely calcified. Proximal occlusion of the aorta should be undertaken as a preliminary operation. This brings about shrinkage of the sac so that at the second operation either the aorta or the common iliac arteries may be ligated immediately distal to the aneurysm.

If the iliac arteries are permanently occluded, care should be taken to see that the ligatures are placed on the common iliacs, not the external iliacs, and the internal iliacs (hypogastrics) should be carefully protected, because of their great importance as collateral channels

Also, all vessels communicating with the sac should be ligated, insofar as possible, before the sac is opened. Only by the employment of meticulous preliminary preparation can one hope for success in such cases

Aneurysms of the proximal portion of the abdominal aorta which have such essential arteries as the celiac, superior mesenteric, or both renals arising from the sac, probably should not be treated surgically, while in those aneurysms arising above the renal arteries but without any of the essential arteries originating from the sac, proximal ligation may be justifiable

BIBLIOGRAPHY

- ¹ Kampmeier, R H Am Jour Med Sci, 192, 97, 1936
- ² Cooper, Sir Astley Reported by Vaughan¹⁰
- ³ James *Ibid*
- ⁴ Murray *Ibid*
- ⁵ Monteiro *Ibid*
- ⁶ South *Ibid*
- ⁷ Stokes, William *Ibid*
- ⁸ McGuire, Hunter *Ibid*
- ⁹ Watson, P H *Ibid*
- ¹⁰ Milton, H *Ibid*
- ¹¹ Korte, W Reported by Halsted¹⁵
- ¹² Keen, W W Reported by Vaughan¹⁰
- ¹³ Tillau *Ibid*
- ¹⁴ Morris, R T *Ibid*
- ¹⁵ Halsted, W S Surgical Papers, 1, 356, 1924 Johns Hopkins Press, Baltimore, Md
- ¹⁶ Halsted, W S *Ibid*, 365
- ¹⁷ Halsted, W S *Ibid*, 418
- ¹⁸ Heuer, George J Reported by Reid²⁰
- ¹⁹ Vaughan, George Tully ANNALS OF SURGERY, 74, 308, 1921, Papers on Surgery and Other Subjects Washington, D C, W F Roberts Company, 94, 1932
- ²⁰ Reid, Mont R Arch Surg, 12, 1, 1926
- ²¹ Watts, Stephen H Personal communication
- ²² Matas, Rudolph ANNALS OF SURGERY, 81, 457, 1925
- ²³ Brooks, Barney J A M A, 87, 722, 1926
- ²⁴ Reid, Mont R Am Jour Surg, 14, 17, 1931
- ²⁵ Andrus, W D Reported by Reid²¹
- ²⁶ LaRoque, G Paul Trans South Surg Assn, 43, 245, 1930
- ²⁷ Bigger, I A Reported in detail in this paper (Discussion of Elkin's Paper ANNALS OF SURGERY, 112, 895, 1940)
- ²⁸ Elkin, D C Personal communication
- ²⁹ Archibald, Edward J A M A, 50, 573, 1908
- ³⁰ Matas, Rudolph Personal communication
- ³¹ Reid, Mont R Personal communication
- ³² Holman, Emile Personal communication
- ³³ Bogoraz, N A Vestnik Khir, 50, 175, 1937
- ³⁴ Brooks, Barney Personal communication
- ³⁵ Lozano, Ricardo La Clinica Moderna (Saragoza), 4, 648, 691, 1905
- ³⁶ Munro, John C New York Med Jour, Phila Med Jour, 85, 681, 1907
- ³⁷ Crile, George W Reported by Matas³⁰
- ³⁸ Kummel Deutsch Med Wchnschr, 40, Part 1, 731, 1914

ANEURYSM OF THE ABDOMINAL AORTA*

TREATMENT BY LIGATION

DANIEL C. ELKIN, M.D.

ATLANTA, GA

FROM THE DEPARTMENT OF SURGERY, EMORY UNIVERSITY, ATLANTA, GA

"ON Sunday, the 12th ult., Mr. James, one of the surgeons of this institution, placed a *ligature* upon the aorta, in a case of *aneurysm* of the external iliac artery. In one of the Exeter papers, it is stated that the operation was 'successfully performed', but it was that kind of success of which the Irishman boasted when he had killed his hog, for the patient survived the infliction of the knife only two or three hours. It is an appalling operation, and we hope not to hear of its repetition—at least in a case of *aneurysm of the external iliac artery* (Lancet, 2, 607, 1828-1829)."

Reports of ligation of the abdominal aorta are rare. Only 24 recorded instances of this operation have been found in the literature, the first by Sir Astley Cooper, in 1817. No doubt others have been performed, but probably without success. In only ten instances was ligation (either complete or partial) performed for aneurysm of the aorta, but was more often undertaken because of aneurysm of the iliac or femoral vessels,¹⁰ gunshot wound of the aorta or its branches,² or tumors.² In two instances, ligation was distal to the seat of the disease, and in 22 proximal to it. In ten cases, the occlusion was complete and in 14, the vessel was purposely only partially occluded at the time of the operation or became so soon afterwards. In only five instances can the procedure be said to have been successful, as judged by the period of survival and the relief of symptoms. The rather tart report of Mr. James' operation in the Lancet would, therefore, seem to be supported by the experience of others.

Vaughan's patient, upon whom a partial, distal ligation was performed, survived for two years, and was to some extent relieved of symptoms. Watts' patient lived three and one-half years, and LaRoque's was living 14 months after operation. In Matas' patient, the occlusion was not complete, and she survived with relief for a year and five months. Brooks completely occluded the aorta for aneurysm, and his patient lived for three months. It is unfortunate that these last two patients died of causes unrelated to the disease or the operation, namely, one from tuberculosis, and the other from intestinal obstruction. Most often, death resulted from shock and hemorrhage within a few hours. However, nine patients were operated upon before the days of listerism, and the first four, without the aid of an anesthetic. Progressively better results give promise of its successful accomplishment more often in the future.

The 24 previously reported cases are reviewed in outline in the accompanying table and the procedure in each instance is diagrammatically illustrated. To these is added another operated upon by me.

* Read before the American Surgical Association, St. Louis, Mo., May 1, 2, 3, 1940.

TABLE I
LIGATIONS OF THE ABDOMINAL AORTA

No	Operator	Date	Publication	Indication	Result	Comment
1	Cooper ¹	1817	Lectures on Surgery Boston, Wells and Lilly, 1825	L iliofemoral aneurysm	Lived 40 hrs	Ligation just above bifurcation At autopsy, aorta sealed with cloth 1 inch above ligature
2	James ²	1825	Med Chr Tr, 16, 1830	L ext iliac aneurysm	Lived 3 hrs	Complete ligation just above bifurcation Pain and deadness in legs
3	Murray ³	1834	London Med Gaz 14, 68, 1834	R iliofemoral aneurysm	Lived 23 hrs	Complete ligation just above bifurcation
4	Monteiro ⁴	1842	Lancet, 1, 334, 1842-1843	R iliofemoral aneurysm	Lived 10 days from hemorrhage—due to infection	Partial occlusion with silk just above bifurcation Satisfactory clotting
5	South ⁵	1856	Lancet, 2, 47, 1856	R common and ext iliac aneurysm	Lived 43 hrs	Ligation at bifurcation First operation performed under an anesthetic
6	McGuire ⁶	1868	Am Jour Med Sci, 56, 415, 1868	Aortic aneurysm extending into both iliacs	Lived 11 hrs	Ligation just below inferior mesenteric artery Rupture of sac required aortic ligation
7	Stokes ⁷	1869	Dublin Quart Jour Med Sci, 48, 1, 1869	R iliofemoral aneurysm	Lived 13 hrs shock	Complete ligation with silver wire at bifurcation Contents of sac clotted Colateral circulation good
8	Watson ⁸	1869	Brit Med Jour, 2, 216, 1869	Iliac aneurysm	Lived 65 hrs	Common iliac tied 9 wks previously Aorta ligated with silk at bifurcation for secondary hemorrhage, ext and int iliacs also ligated Because of bleeding—aorta ligated by mistake for common iliac Circulation good on right
9	Czerny ⁹	1870	Wien med Wehnschr, 1, 402, 1870	Wound of left femoral artery	Lived 27 hrs sepsis and hemorrhage	Severe hemorrhage from renal artery necessitated ligation of aorta and left renal artery
10	Czerny ¹⁰	1879	Centralbl f Chir, 6, 737, 1879	Tumor of left kidney	Lived 10 hrs	Ligation with silk below renal vessels for ruptured aneurysm
11	Milton ¹¹	1890	Lancet, 1, 85, 1891	Ruptured aortic aneurysm	Lived 24 hrs hemorrhage and shock	Partial ligation just below diaphragm Gradual reduction in size
12	Keen ¹²	1899	Am Jour Med Sci, 120, 251, 1900	Aortic aneurysm	Lived 48 days from cutting of ligature	

LIGATION OF ABDOMINAL AORTA

13	Korte ¹³	1899	Deutsche med Wchnschr , 26, 717, 1900	R common iliac aneu- rysm	Lived 1 hr	Common iliac ligated 37 days previously Aorta ligated with silk at bifurcation Death from hemorrhage
14	Tillaux ¹⁴	1900	Bull et Mém Soc de Chir de Paris, 1900	L iliac aneurysm	Lived 39 days Femoral vein thrombosed	Partial ligation, ligature slipped Aorta ligated by mistake for common iliac
15	Morris ¹⁵	1901	ANNALS OF SURGERY, 35, 207, 1902	Aortic aneurysm extend- ing from celiac axis to mesenteric vessels	Lived 53 hrs Gangrene of intestine from pres- sure of clamps	Partial distal ligation by cath- eter held with clamps
16	Scott ¹⁶	1905	Hosp Bull Univ Mary- land, 1, 41, 1905	Gunshot wound of adom- inal aorta	Died—1 hr	Ligation with catheter and forceps just above bifurca- tion
17	Halsted ¹⁷	1906	Surgical Papers, 1, 321, 1924	Aneurysm of abdominal aorta	Death—18 days after sec- ond band Rupture in- trathoracic	Band applied to thoracic aorta 23 days later, band applied to abdominal aorta distal to aneurysm
18	Halsted ¹⁸	1909	Surgical Papers, 1, 321, 1924	Aneurysm of abdominal aorta	Death from infection—47 days after band was placed	Band applied between renal and sup mesenteric arteries Later wired
19	Hamann ¹⁹	1917	ANNALS OF SURGERY, 68, 217, 1918	Tumor of pelvis	Lived 6 mos Death from hemorrhage from bed sore	Ligation just above bifurca- tion At autopsy, aorta only partially occluded
20	Vaughan ²⁰	1920	ANNALS OF SURGERY, 74, 308, 1921, also 76, 519, 1922	Aneurysm of abdominal aorta at origin of sup mesenteric artery	Lived 2 yrs and 1 mo	Distal ligation with cotton tape Apparently improved during life Autopsy showed partial occlusion
21	Watts ²¹	1923	Trans South Surg As- soc , 43, 245, 1931 (quoted by LaRoque ²¹)	R common iliac aneu- rysm	Lived 3½ yrs	Partial ligation with tape just below sup mesenteric artery Improvement Death due to rupture
22	Matas ²²	1925	ANNALS OF SURGERY, 81, 457, 1925	Aneurysm of abdominal aorta at bifurcation	Lived 1 yr 5 mos Died of tuberculosis	Double complete ligation, with cotton tape, at bifurcation Sac clotted but not com- pletely occluded First suc- cessful ligation
23	Brooks ²³	1926	J A M A , 87, 722, 1926	Aneurysm of abdominal aorta at bifurcation	Lived 3 mos Died in- testinal obstruction	Complete ligation with fascia and silk just above bifurca- tion Apparently cured
24	LaRoque ²⁴	1929	Trans South Surg, As- soc , 43, 245, 1931	R common iliac aneu- rysm	Living 14 mos after op- eration	Partial ligation with silk and cotton tape at bifurcation
25	Elkin ²⁵	1939	ANNALS OF SURGERY, 112, 895, 1940	Aneurysm of abdominal aorta at bifurcation	Alive 11 mos after oper- ation Improved	Double partial ligation with tape proximal to aneurysm Reduction in size Brut present

Case Report—Hosp No 90842 J E C, white, male, age 61, a minister, was admitted to the Emory University Hospital, May 28, 1939, complaining of a tumor in his abdomen and of pain in his legs. His past health had always been good. His mother, father and two brothers died of cardiovascular disease.

About six months previously, he had noticed a swelling in the left side of his abdomen but paid little attention to it since it was not causing pain. The mass grew progressively larger, and the pain, which was at first intermittent, became constant, and was of such severity as to keep him awake. The pain extended over his lower abdomen and into his

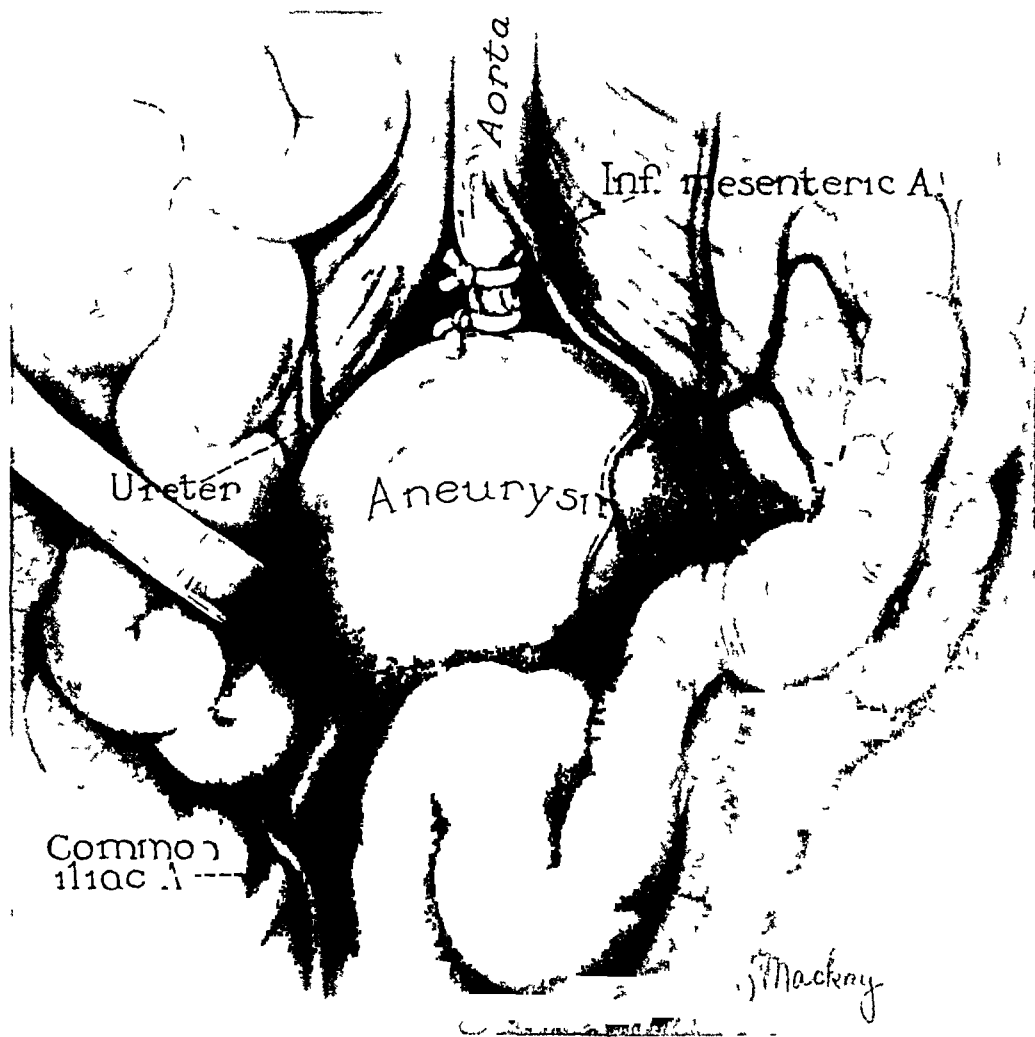


FIG 1—The appearance of the aneurysm at operation. Double ligation with cotton suture between the inferior mesenteric artery and the bifurcation.

legs. He occasionally had severe "cramps" in the calves of his legs. His feet were colder than normal, and numbness and tingling were frequently experienced. During the month preceding examination, he had noticed that the abdominal mass pulsated.

Physical Examination—There was a marked thickening and tortuosity of his peripheral vessels. His heart was normal in size. There were occasional extrasystoles. In the lower abdomen, a rounded mass could easily be felt. It was about five inches in diameter with its upper margin at the level of the umbilicus. It pulsated synchronously with the heart beat. There was no thrill and no bruit. The circulation in his legs was good, the femoral, popliteal, dorsalis pedis and posterior tibial vessels were pulsating. His blood pressure at the cubital fossa was 140 systolic and 100 diastolic. The pressure in the popliteal vessels was approximately the same.

Roentgenologic examinations showed arteriosclerosis of the aorta and the peripheral vessels. There was some calcification in the abdominal mass, which could be seen pulsating under the fluoroscope. The Wassermann and Kahn reactions were negative.

Operation—June 1, 1939. Under cyclopropane and ether anesthesia. The abdomen was opened through a left rectus incision. The aneurysm was immediately disclosed. It occupied the lower aorta from a point just below the inferior mesenteric artery to the bifurcation. The dilatation extended slightly into both common iliac arteries. Calcified plaques could be felt in the aneurysm and in the aorta above it. The posterior peritoneum was opened through an avascular area, and the aorta was dissected free of its surrounding tissues at a point just below the origin of the inferior mesenteric artery. This was difficult because of the calcification of the vessel and its adherence to the surrounding tissues. When the aorta was completely isolated, it was partially ligated at two places with one-fourth inch cotton tape (Fig. 1). The ligatures were placed about one-half inch apart. The tapes were tied until the pulsation in the aneurysm was almost completely obliterated and until the pulsation of the femoral vessels could scarcely be felt. Since there was no increased vascularity about the aneurysm and no evidence of a compensatory collateral circulation, it was thought best to only partially occlude the circulation to the extremities. Moreover, the marked arteriosclerosis of the peripheral vessels seemed to make complete ligation unwise. The peritoneum was closed over the ligatures and the abdomen closed in layers.

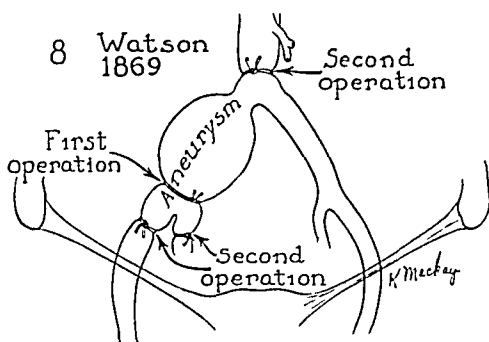
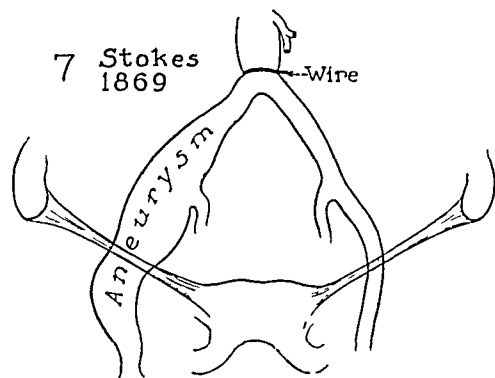
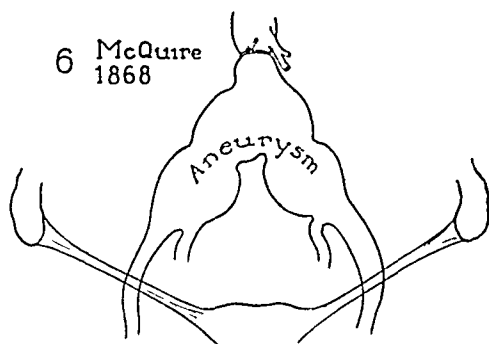
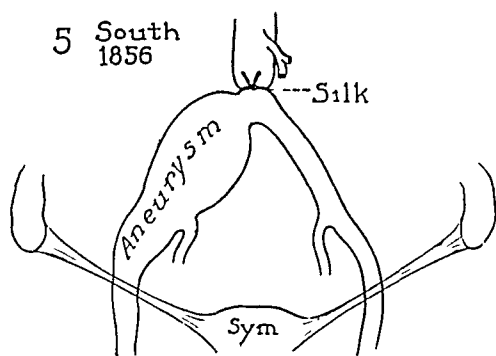
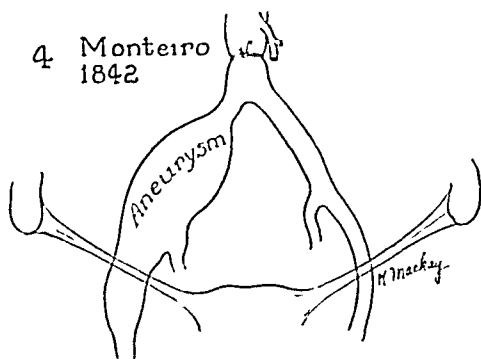
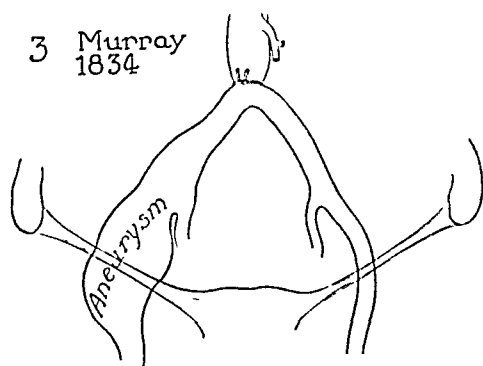
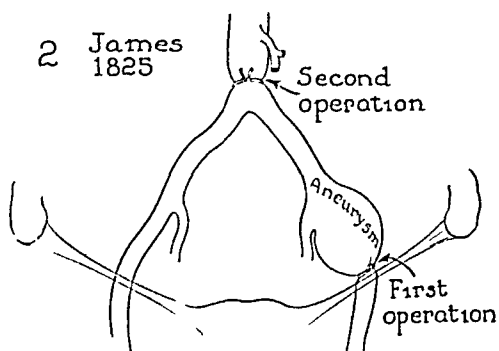
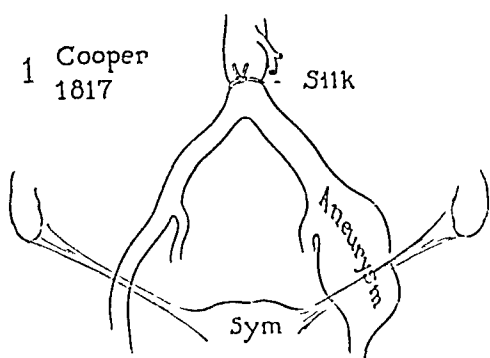
Postoperative Course—There was no remarkable change in the heart sounds following this ligation. The systolic blood pressure gradually rose during the operation from 140 to 180 and the diastolic from 90 to 100. The rate of the pulse and respirations was not remarkably affected (Fig. 2). Following operation, he complained of some coldness in his legs but this disappeared in two days. The systolic blood pressure in the popliteal vessels dropped to 60 Mm Hg. Within a week, he was completely relieved of pain in his abdomen and legs. He was allowed out of bed on the twelfth day and returned home, two weeks after operation. At this time, the mass was considerably smaller and could be felt only as an area of induration in the left lower quadrant. There was no pulsation, no thrill, and no bruit. Within a month he resumed his duties as a country minister and since that time has been actively engaged in his work. He drives a car daily without difficulty.

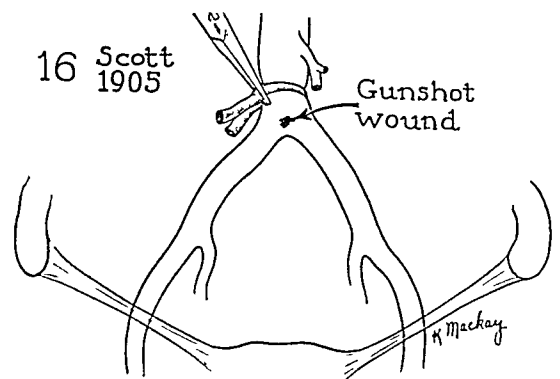
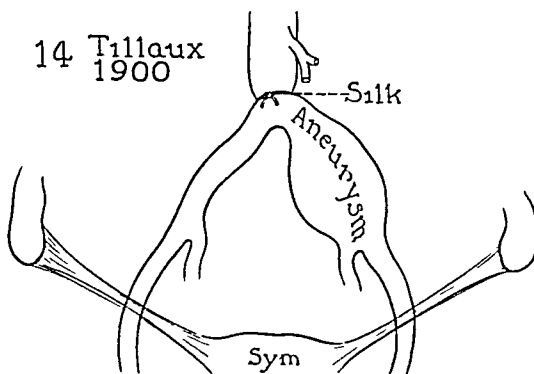
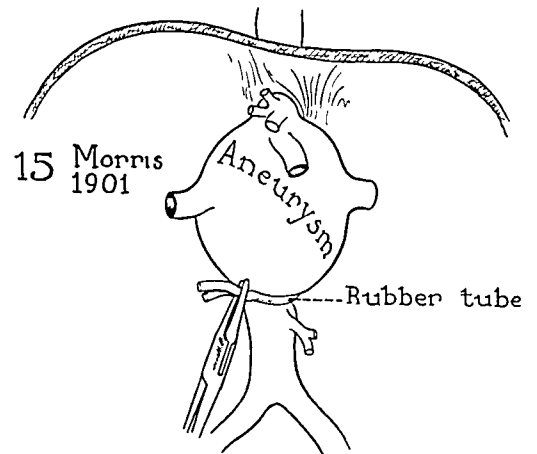
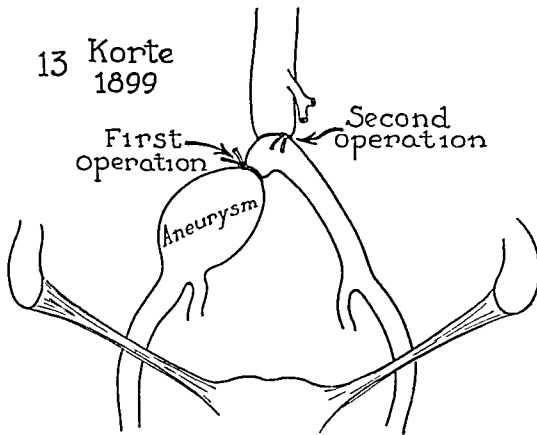
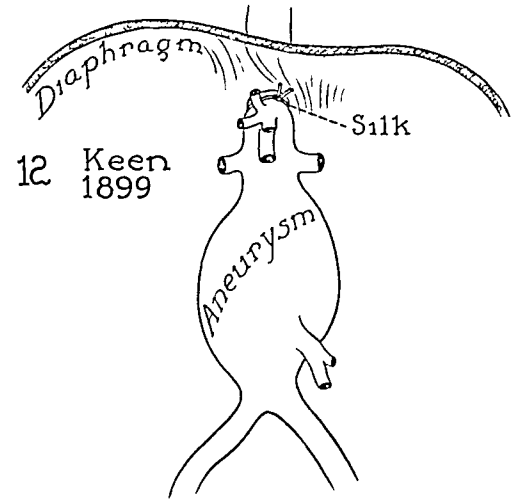
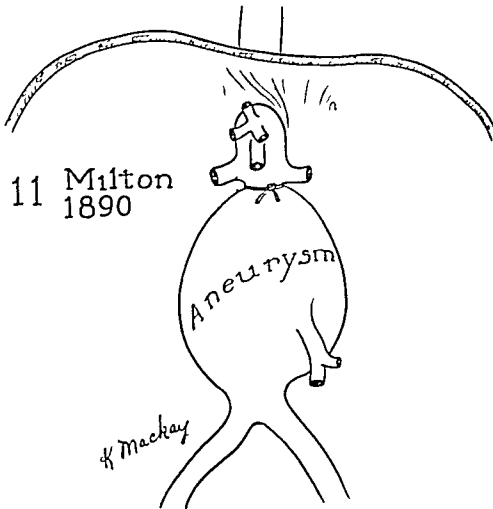
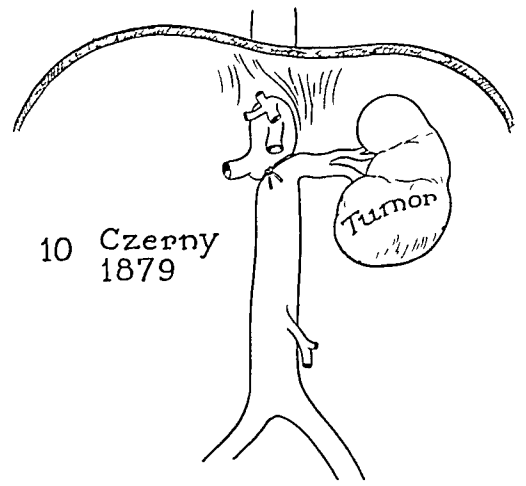
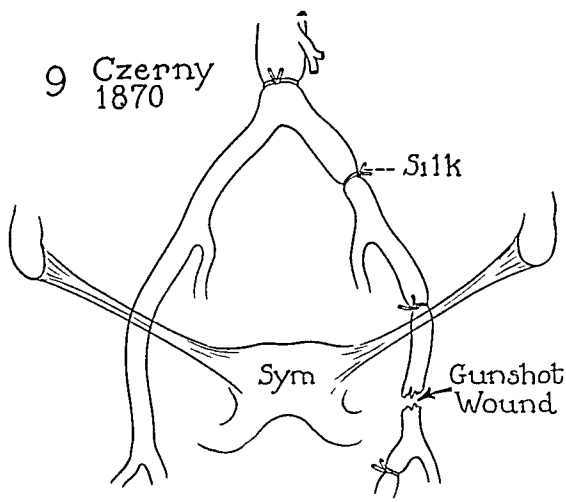
Six months later the mass could be felt but was much smaller than originally. There was a slight pulsation in it and a definite systolic bruit could be heard over it. Since that time, there has been no change in the mass and, now, 11 months after operation, he is free from pain and able to carry out his duties. The pulsation in the femoral artery is forceful, but the pulsation in the dorsalis pedis and posterior tibial arteries is weak and inconstant. It would appear that the partial ligation has so slowed the current of blood through the aneurysm as to bring about partial clotting but complete occlusion has not been accomplished.

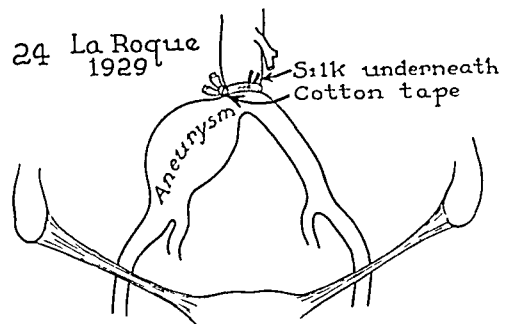
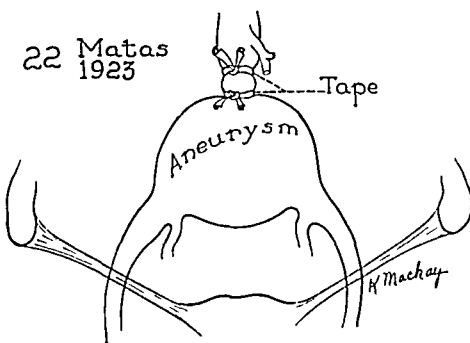
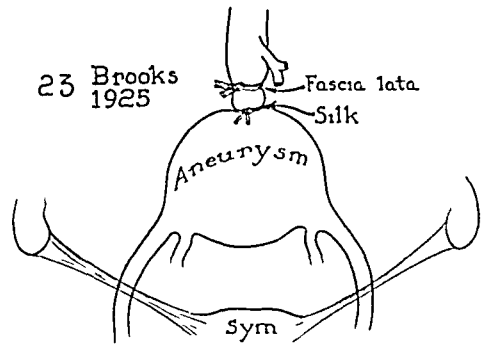
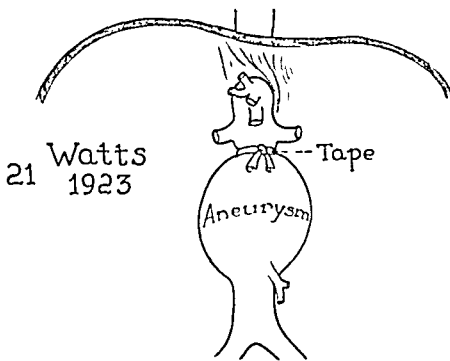
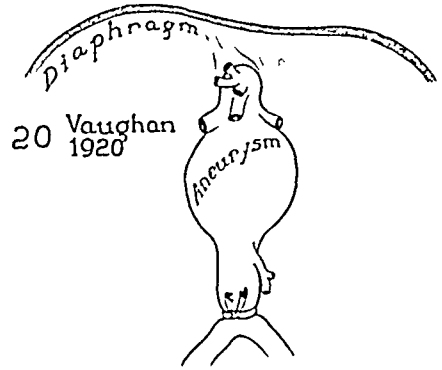
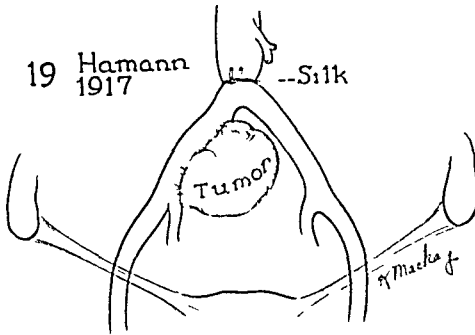
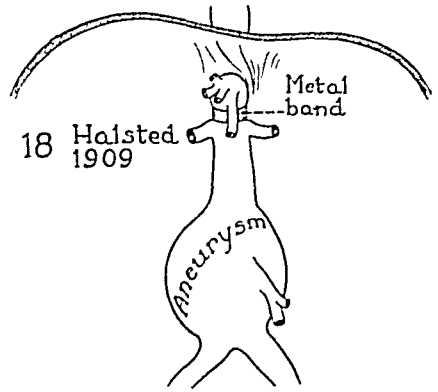
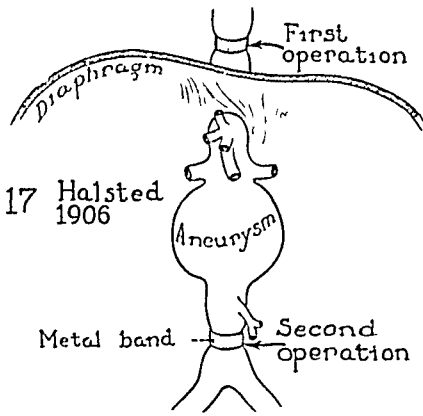
There are certain inherent difficulties in ligation of the aorta aside from its technical performance. This probably accounts for the small number of attempts to occlude the vessel.

(1) *The location of the aneurysm* is rarely at a point where proximal ligation can be undertaken without menace to the vitality of the kidneys or intestine. The most frequent site is in the region of the celiac axis, and partial distal ligation is usually the only procedure that can be carried out. Theoretically, this may slow the blood current and produce clotting and delay rupture, as in Vaughan's case, but, practically, it is rarely successful.

Only rarely is an unruptured aneurysm found at the bifurcation and in such a position that the aorta can be occluded distal to the inferior mesenteric

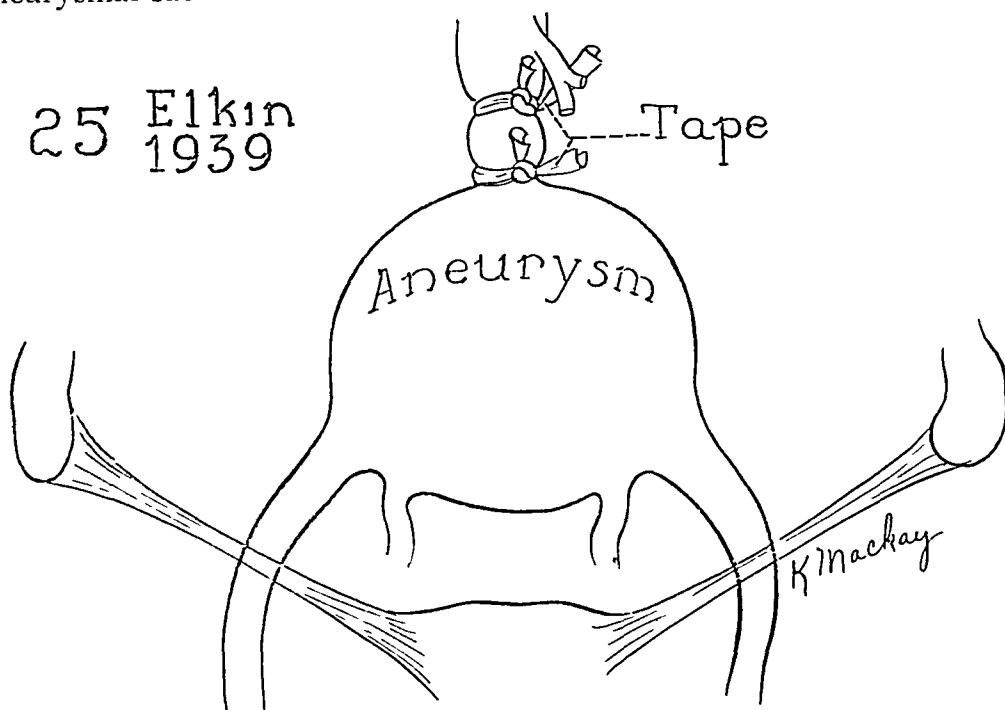






artery Complete ligation above that vessel would, very likely, result in gangrene of the sigmoid

(2) *An efficient collateral circulation rarely exists about an aortic aneurysm, and gangrene of the extremities will result if the vessel is occluded* In only one instance (Brooks²³) had the communications developed sufficiently to allow the surgeon to completely occlude the vessel Moreover, this same collateral supply may be the cause of an early recurrence as vessels reenter the aneurysmal sac



(3) *The type of ligature and the manner of occlusion still remain an unsolved problem* Partial occlusion with metal bands (Halsted^{17, 18}) or with silk or wire is usually unsuccessful because of the danger of rupture of the vessel at the point of ligature Bands of fascia or tape frequently give way and allow the channel to reopen Partial double ligation plus the introduction of some sclerosing substance may overcome these disadvantages

(4) *The effect on the heart* has been the subject of considerable dispute Kast,²⁶ in 1880, concluded, from a series of experiments, that the blood pressure in the aorta did not rise proximal to the point of ligation It was his opinion that the effect on the heart was not dangerous to life However, Katzenstein,²⁷ in 1905, formed exactly the opposite opinion since he found an elevation in the blood pressure of the artery proximal to the site of the occlusion and dilatation and hypertrophy of the heart Matas²² believed that total occlusion of the abdominal aorta imposed a strain upon the heart In Brooks' case the heart was found to be essentially normal three months after the ligation of the aorta, but in this instance a considerable collateral circulation was already established

Brooks, Blalock and Johnson²⁸ found, following a series of experiments in dogs, that the cardiac output was decreased and there was little, if any, change in the blood pressure proximal to the occlusion They found no evidence of hypertrophy of the heart

In the case here reported, there was a gradual rise in the blood pressure throughout the operation. A continuation in this rise following partial occlusion of the aorta cannot, therefore, be attributed to the occlusion of the vessel (Chart 1)

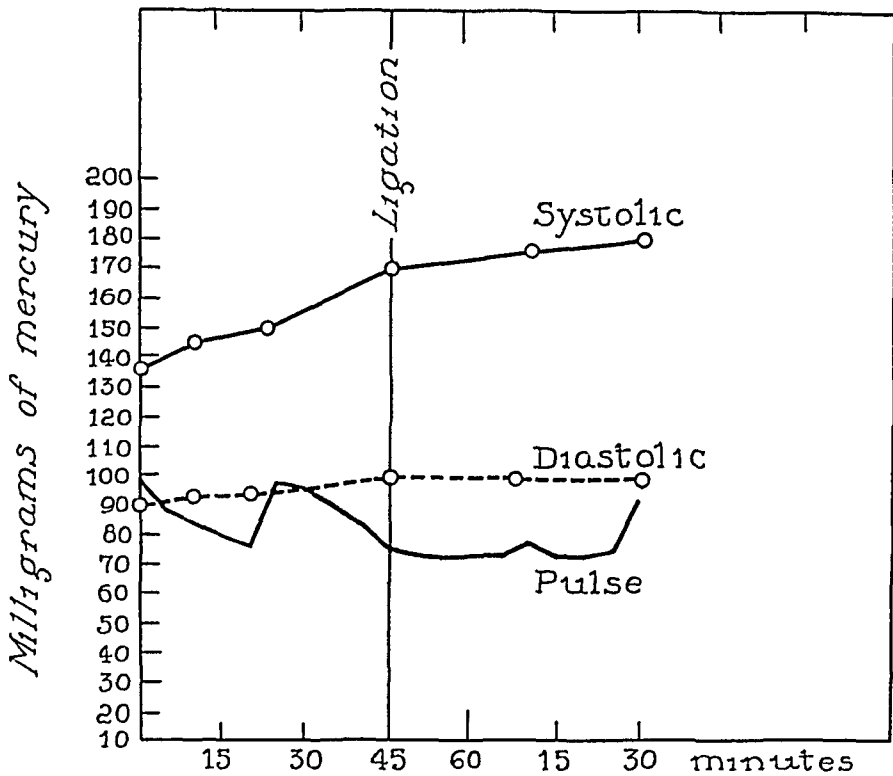


CHART 1—Showing the systolic and diastolic blood pressure and the pulse during operation. The rise in blood pressure was gradual throughout and therefore could not be attributed to the ligation of the aorta.

Recently, the opportunity to observe the effect in another patient was offered (Chart 2). In this case the aortic aneurysm in the region of the celiac axis was treated by distal ligation just above bifurcation. There was no change in the blood pressure for 15 minutes. After 15 minutes there was a sudden drop of systolic pressure from 120 to 80 with evidence of circulatory failure. Following stimulation and a lowering of the patient's head the blood pressure rose, in about 30 minutes, back to 120 and was maintained at this level until rupture of the aneurysm produced death two days later. It was thought that this sudden fall in blood pressure was due to cardiac failure but why this should occur without previous rise in arterial pressure is not understood.

Discussion—This report is concerned primarily with the effects of ligation of the abdominal aorta and consideration of those cases in which this procedure has been carried out. Therefore, the treatment of aortic aneurysm by other methods has not been considered. In only six patients, upon whom ligation has been performed, may the procedure be considered in any degree successful. Other means of treating an aneurysm of this vessel should be considered, but it is improbable that wiring, coagulation, or the application of the Matas principle of endo-aneurysmorrhaphy could be carried out with any great hope of

success The effect upon the heart and circulation should be further studied and methods of producing occlusion by other means than ligation must be developed before the operation can be successfully performed in the majority of cases

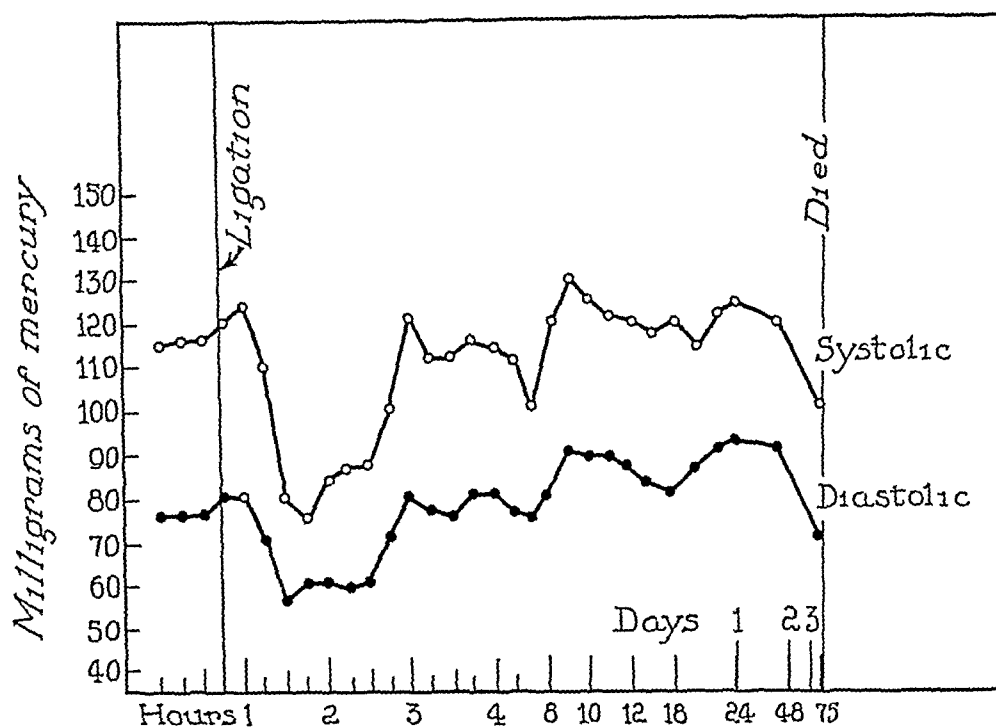


CHART 2—Showing the systolic and diastolic pressure in a patient upon whom the aorta was ligated distal to the aneurysm. Note the marked drop in blood pressure after ligation. This was attributed to cardiac failure.

BIBLIOGRAPHY

- ¹ Cooper, A. Lectures on Surgery. Boston, Wells and Lilly, 2, 56, 1825.
- ² James, J. H. Case of Aneurysm of the External Iliac Artery, for Which the Femoral Artery and Subsequently the Aorta Were Tied. Med Chir Tr, London, 16, 1, 1830.
- ³ Murray, J. Ligature of the Abdominal Aorta. London Med Gaz, 14, 68, 1834.
- ⁴ Monteiro, C. B. Abdominal Aorta Tied (Correspondence). Lancet, 1, 334, 1842-1843.
- ⁵ South. Very Large Aneurysm of the External and Common Iliac Arteries, Occupying a Considerable Portion of the Right Half of the Abdomen, Formidable Operation of Deligation of the Abdominal Aorta Just Above Its Bifurcation, Survival of the Patient 43 Hours. Lancet, 2, 47, 1856.
- ⁶ McGuire, H. Aneurysm of External Iliac of the Left Side, Both Common Iliacs, and Lower End of Aorta, Ligation of the Aorta—Death. Am Jour Med Sci, 56, 415, 1868.
- ⁷ Stokes, W., Jr. On Temporary Deligation of the Abdominal Aorta. Dublin Quart Jour Med Sci, 48, 1, 1869, Brit Med Jour, 1, 270, 1869.
- ⁸ Watson, J. H. Ligature of the Abdominal Aorta. Brit Med Jour, 2, 216, 1869.
- ⁹ Czerny. Wien med Wchnschr, 1, 402, 1870 (cited by Morris¹⁴).
- ¹⁰ Czerny. Über Nierenexstirpation. Centralbl f Chir, 6, 737, 1879.
- ¹¹ Milton, H. Ligature of the Abdominal Aorta for Ruptured Aneurysm of That Vessel—Death. Lancet, 1, 85, 1891.
- ¹² Keen, W. W. A Case of Ligature of the Abdominal Aorta Just Below the Diaphragm—the Patient Surviving for 48 Days. With a Proposed Instrument for the Treatment of Aneurysm of the Abdominal Aorta by Temporary Compression. Am Jour Med Sci, 120, 251, 1900.
- ¹³ Korte, W. Ein Fall von Aneurysma der Arteria iliaca externa mit Berstung und consecutiver Unterbindung der Arteria iliaca communis und Aorta. Deutsche med Wchnschr, 26, 717, 1900.

- ¹¹ Jillaux. Aneurysme diffus consecutif de l'artere iliaque externe, ligature de l'aorte mort au trente-neuvieme jour Bull et Mem Soc de Chir de Paris, n s 26, 473, 1900
- ¹² Morris, R T Ligation of the Abdominal Aorta for Aneurysm ANNALS OF SURGERY, 35, 207, 1902
- ¹³ Scott, W D Ligation of Abdominal Aorta for Gunshot Wound Hosp Bull Univ Maryland, 1, 41, 1905
- ¹⁴ Halsted, W S Clinical and Experimental Contributions to the Surgery of the Thorax In Surgical Papers, Baltimore, Johns Hopkins Press, 1, 321, 1924
- ¹⁵ Halsted, W S Clinical and Experimental Contributions to the Surgery of the Thorax In Surgical Papers, Baltimore, Johns Hopkins Press, 1, 321, 1924
- ¹⁶ Hamann, C A Ligation of the Abdominal Aorta ANNALS OF SURGERY, 68, 217, 1918
- ¹⁷ Vaughan G I (a) Ligation (Partial Occlusion of the Abdominal Aorta for Aneurysm ANNALS OF SURGERY 74, 308 1921 (b) Ligation of the Aorta, Necropsy Two Years and One Month After Operation ANNALS OF SURGERY, 76, 519, 1922
- ¹⁸ Watts, S Report of a Case of Aneurysm of the Abdominal Aorta Trans South Surg Assoc 43, 245 1931 (quoted by LaRoque.)
- ¹⁹ Matys, R Ligation of the Abdominal Aorta, Report of the Ultimate Result—One Year, Five Months and Nine Days after Ligation of the Abdominal Aorta for Aneurysm at the Bifurcation ANNALS OF SURGERY, 81, 457, 1925
- ²⁰ Brooks, B Ligation of the Aorta, A Clinical and Experimental Study J A M A, 87, 722, 1926
- ²¹ LaRoque, G Paul Ligation of Abdominal Aorta for Aneurysm of the Common Iliac Artery Trans South Surg Assoc, 43, 245, 1931
- ²² Elkin, D C Aneurysm of the Abdominal Aorta ANNALS OF SURGERY, 112, 895, 1940
- ²³ Kast, A Die Unterbindung der Bruchaorta Deutsche Ztschr f Chir, 12, 405, 1879
- ²⁴ Katzenstein, M Die Unterbindung der Aorta, ihre physiologische und ihre therapeutische Bedeutung Arch f klin Chir, 76, 581, 1905
- ²⁵ Brooks, B, Blalock, A, and Johnson, G S Ligation of the Terminal Abdominal Aorta, An Experimental Study Arch Surg, 17, 794, 1928

DISCUSSION —DR I A BIGGER (Richmond, Va) I wish to congratulate Doctor Elkin on his excellent presentation of this interesting case. In this discussion, I would like to emphasize certain points regarding the decision as to whether or not ligation should be attempted in patients with abdominal aortic aneurysms. If one of the essential vessels, such as the superior mesenteric, comes off from the aneurysmal sac, it seems obvious that no curative procedure should be attempted. In other words, it would seem to me that complete proximal occlusion of the aorta in the presence of an aneurysm involving the origin of one of these vessels is worse than useless, for obliteration of the sac by clot will produce occlusion of the superior mesenteric or the celiac arteries which will almost certainly prove fatal.

There is some doubt, I think, as to whether a proximal ligation can be considered more than a palliative procedure in the great majority of cases of aneurysm, although there have been, as pointed out by Doctor Elkin, some instances of apparent cure by proximal ligation alone. In spite of this, it seems likely that the incidence of cure of aortic aneurysm from proximal ligation will be small. Because of this impression, we were not content with proximal ligation in the following case.

About 18 months ago we operated upon a man, age 25, for a ruptured traumatic aneurysm of the abdominal aorta. At the first operation we occluded the aorta proximal to the aneurysm and above the inferior mesenteric artery. It has been shown that occlusion of the inferior mesenteric artery is not likely to be followed by serious interference with the circulation to the segment of bowel supplied by that vessel. After one month we again operated upon this patient and performed an endo-aneurysmorrhaphy.

Following occlusion of the aorta, this man developed complete paralysis of his lower extremities, which persisted for about two weeks and then gradually improved. He also had marked sensory changes which cleared up after about six weeks and he now has excellent function in his lower extremities.

A heavy strip of fascia lata was used for the occlusion, for the reason that we had in mind to attempt endo-aneurysmorrhaphy, and we felt that it would be desirable to have a reestablishment of the circulation through the aorta after the sac had been obliterated. This has occurred, and he now has normal pulsations in all of the vessels of the lower extremities. No evidence of recurrence of the aneurysm can be found.

I realize of course, that a traumatic aneurysm in a young man is an entirely different problem from that presented by spontaneous aneurysms which usually occur in more elderly people, but I do believe that there are some patients with spontaneous aneurysms of the distal portion of the aorta in whom aneurysmorrhaphy might be successful, if undertaken in stages.

If such an operation is to be attempted, it would seem wise to perform a preliminary subtotal occlusion of the aorta proximal to the aneurysm. After a reasonable time, say a month or six weeks, when the sac has become shrunken, an occlusion of the vessel or vessels distal to the aneurysm can be more readily accomplished. After the collateral circulation has been controlled, in so far as possible, some modification of the Matas operation should be performed. This should offer a greater chance of cure than proximal ligation alone.

In spontaneous aneurysms, restorative aneurysmorrhaphy would not be possible, so tape, or similar material, should be used to produce permanent occlusion of the aorta both proximal and distal to the sac.

DR. RUDOLPH MATAS (New Orleans, La.) As a pioneer in this field, I heartily congratulate Doctors Elkin and Bigger on their successful operation for the cure of abdominal aneurysms. They have brought a note of cheer and encouragement to the classically somber tone of aortic surgery.

Taken together with Doctor Owings' experimental success in the segmental obliteration of the lower thoracic and abdominal aortic tract by his method of gradual occlusion, these actual clinical achievements would suggest that surgery is gradually approaching some mastery over one of its most rebellious provinces.

Doctor Elkin's case appeals to me particularly because his experience duplicates and largely confirms the value of the technic adopted in the successful ligation of the aorta for an aneurysm of the bifurcation and iliacs which I reported to the Association at Baltimore in 1924. In that case, the occlusion was complete when applied, but became partial on the ninth day, when the pulsation returned in the sac showing that the ligatures had yielded sufficiently to allow a small stream to flow through a narrow channel in the ligated segment. While this reduced stream gave great relief to the cardio-pulmonary circulation and no doubt saved the patient's life, it did not prevent the ultimate cure of the aneurysm because this had been completely consolidated by laminated clot and had ceased to pulsate long before her death, which occurred one year and five months after the ligation, consequent to an overwhelming hemorrhage from a tuberculous cavity in the lung.

Doctor Elkin used two cotton tapes, as I did, and I presume, from his patient's excellent recovery, they were as well tolerated by the aorta of his patient. For as I will show later, the histology of the ligated segment demonstrated that contrary to the usual experience the tapes had not cut through but had been completely incorporated in the walls of the artery without injuring the intima in the least. The ligated segment was entirely covered by a capsule of dense connective tissue which blended perfectly with an external

coat of the aorta, greatly strengthening the artery while completely concealing the ligatures. Judging by the histologic study of the ligated segment of the aorta in my patient's case and by Doctor Elkin's success, cotton tape, which was first used to ligate the aorta by Dr G T Vaughan of Washington, at Doctor Halsted's suggestion (with survival of more than two years), is a dependable material and, in fact, is so well tolerated and assimilated by the aortic walls that it would seem to make the use of autogenous fascial and other organic tissue material a thoroughly unnecessary and superfluous performance. Our experience with cotton tape would seem to bear out the general conclusions of Meade and Ochsner (1940) in making cotton a preferable material for buried sutures and ligatures.

I am very much obliged to Doctor Elkin for the pains he has taken to illustrate the procedure adopted in my patient's case. His drawings will serve as an appropriate introduction to the lantern slides exhibit that is to follow this discussion.

Doctor Bigger's operation is also of special interest to me as it is the first successful application to the aorta of my method of intrasaccular suture (endoaneurysmorrhaphy) for the cure of aneurysm. We have records of five endoaneurysmorrhaphies for abdominal aortic aneurysms (R Lozano 1905, J C Munio, 1906, G W Cile, 1907, J H Gibbon, 1912), all of which ended fatally, except the last operation performed by Doctor Bigger, January 10, 1939. All of these operations were performed under desperate and seemingly hopeless circumstances for ruptured or leaking sacs, two dying on the table and the two others surviving only a few hours. Doctor Bigger's patient is the only traumatic aneurysm caused by gunshot wound. The history of this complicating injury, as related by Doctor Bigger, is a fine example of the resourcefulness of contemporary surgery under good generalship, especially since unlimited blood transfusion has become so universally available, besides the benefits of autotransfusion, which was a feature of this difficult case.

In addition to the five abdominal aneurysmorrhaphies, there are two cases of thoracic aneurysms in which the method of suture has been resorted to. One, a traumatic aneurysm of the descending thoracic aorta on which Kummel, of Hamburg, performed a constructive aneurysmorrhaphy (1914), technically a fine success, but unfortunately in a hopeless condition. The other is a sacculated aneurysm of the ascending arch of the aorta, reported by V V Kerstorsky (1927), in which the sac was torn in the course of an intrathoracic exploration. An immense hemorrhage flooded the field, which was controlled by clamping the broad pedicle of the sac, thereby excluding it from the arch of the aorta, the exclusion of the sac being completed by a series of continued mattress sutures. Hemostasis was secured, but the patient was so depleted by hemorrhage and shock that he died on the table before he could be transfused.

Other cases could be quoted from the recent literature which indicate that thoracic surgeons, emboldened by the great progress in the technic of pulmonary surgery, are making more frequent attempts to explore for aneurysm of the aorta and heart, in the hope that a sacculated aneurysm may be found in its early stages which will lend itself to conservative methods of suture. Thus far, the great majority of all these attempts in the thorax have proved abortive, usually ending with an exploration or with some heroic episode which has not encouraged many renewals of the same experience.

We may safely assert that, for the present, at least, the hope of aneurysmal therapeutics in the chest must depend much more on prophylaxis than on surgery, including the recently attempted resurrection of the methods of wiring and electrolysis.

ANEURYSM OF THE ABDOMINAL AORTA AT ITS BIFURCATION INTO THE COMMON ILIAC ARTERIES*

A PICTORIAL SUPPLEMENT ILLUSTRATING THE HISTORY OF CORINNE D ,
PREVIOUSLY REPORTED AS THE FIRST RECORDED INSTANCE OF CURE
OF AN ANEURYSM OF THE ABDOMINAL AORTA BY LIGATION

RUDOLPH MATAS, M D

NEW ORLEANS, LA

THE HISTORY of this aneurysm, and of the ligation of the abdominal aorta performed for its cure, was originally presented, as a preliminary report, before the American Surgical Association at its meeting in Baltimore, April 18, 1924 (Ti Am Surg Assn , 42, 603-616, 1924), and in the ANNALS OF SURGERY, 81, 457-464, February, 1925

The last report closed with a statement that a final, illustrated report of the case, in all its bearings, would appear in a later publication. Unfortunately, a number of circumstances delayed the completion of the final report, but out of the abundance of the illustrative material which had collected about this patient, a moving picture was made which showed the patient, the aneurysm the technic of the ligation, and all the gross anatomic and histologic changes in the artery at the site of the ligation. This film was exhibited by the writer at the Dallas meeting (surgical section) of the American Medical Association in April, 1926, at the discussion of Dr Barney Brooks' report of a successful aortic ligation for a similar aneurysm. This demonstration passed in silence, and the film was not included in the published proceedings of the meeting. Through some unaccountable accident, the film was destroyed or lost while in storage at the promoters' laboratories. However, the original drawings, photographs and other illustrations were, fortunately, preserved in the library of the Medical School (Tulane), and it is from this source that the film exhibited by the writer at the St. Louis discussion of Doctors Elkin's and Bigger's successful ligations was made available for that occasion.

In view of the historic interest attached to the case of the patient, Corinne D , as the first recorded cure of an aneurysm of the abdominal aorta by ligation, and of the fact that the ligatures—contrary to previous experience—were made effective without cutting through the artery or damaging its coats, it would seem that the hitherto unpublished photomicrographs and drawings of the anatomic and histologic changes in the walls of the aorta at the site of its ligation would fit into the discussion of the successful cases of Doctors Elkin and Bigger, if only as an instructive illustration of the gradual evolution of a working technic of aortic surgery in the abdomen, as it was so encouragingly unfolded at this meeting. Besides, and quite apart from any historic interest,

* Introduction to a moving picture of the case of Corinne D , exhibited in the discussion of "Aortic Aneurysms" (Doctors Elkin and Bigger) at the meeting of the American Surgical Association, St. Louis, May 1-3 1940

the series of illustrations which are herewith reproduced, will, I trust, help to redeem the promise of their publication made 13 years ago

SYNOPTIC HISTORY OF THE PATIENT WITH A RECAPITULATION OF THE
MORE SALIENT FACTS AND CONCLUSIONS

Case Report—*Corinne D.*, colored, female, age 28, field laborer First admitted to Charity Hospital, (Dr J B Guthrie's clinic), October 25, 1922



FIG 1—*Corinne D.*, age 29 Aneurysm of the common iliac arteries including the bifurcation of the aorta Photograph of the patient one year after the ligation of the aorta Right hip partially ankylosed as a result of arthritis and contracture of the muscles of the foot and leg by edema, due to compression of the anterior crural nerve and right common iliac vein Good circulation in the upper and lower extremities despite low blood pressure and feeble pulses

Diagnosis—Malignant syphilitic infection with generalized manifestations—eight months' duration before admission (fever, acute polyarthropathies and myalgias specially localized in lumbar spine, hip, knee and other joints of the lower extremities, general adenopathy, tibial periostitis and multiple suppurating syphilides on legs, arm and body)

ANEURYSM OF ABDOMINAL AORTA

Wassermann strongly positive A helpless and crippled invalid when admitted Under vigorous antisyphilitic treatment, was so much improved that, by December 16, 1922, she considered herself well and was discharged at her own request

Readmitted March 6, 1923 (service of Drs E D Martin and A C King) Neglected treatment, and relapsed into a worse condition than on first admission In addition to the

FIG 2

FIG 3

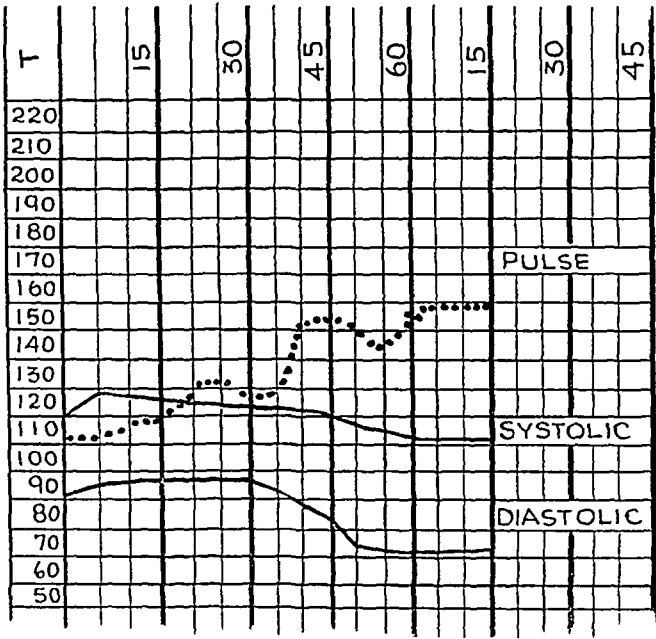
FIG 4



FIG 2 —Teleradiograph of pelvis, April 4, 1923, five days before the ligation of the aorta

FIG 3 —Teleradiograph of pelvis nearly two months after ligation of the aorta The shadows over the sacroiliac region extending into the right sacro sciatic notch and over the sacrum obscure the outlines of the bone The right half of the pelvic cavity is also obscured by the ill defined shadow of the sac as it was beginning to fill with clot The erosion of the left trochanter from syphilitic osteo periostitis is also plainly shown

FIG 4 —Teleradiograph of pelvis, March 27, 1924, nearly one year after the ligation of the aorta showing marked reduction in the aneurysmal shadow



ANESTHETISTS CHART Corinne D ligation of abdominal aorta, 1/9/23 Dr Allgeyer anesthetist—Gas oxygen Preliminary morph sulph gr ¼ + atropine sulph gr 1/150 Anesthesia commenced at 9 08 A M Operation commenced 9 28 A M Anesthetic discontinued 10 30 A M , operation 10 30 A M Note rise of pulse and dropping of blood pressure on ligation of the aorta, 45 minutes after beginning of operation, and persistent high pulse rate (155 160) after the ligation, with notable increase in the respiratory rate after the ligation (24 38)

arthropathies which crippled her spine, right hip and other parts of her lower extremities, she had developed an aortic aneurysm (a sequela to an acute aortitis) which involved both common iliacs and the aortic bifurcation Coincidentally with the relapse in the arthropathies of the spine, hip and other parts of the lower extremities and the appearance of the pulsating tumor, a remittent fever had developed ranging from 100° to 104°+ F, which at first suggested a retroperitoneal abscess This diagnosis was dismissed as the fever gradually subsided, leaving the aneurysmal tumor growing visibly, and rapidly, with increasing lumbar and radiating pressure pains in the pelvis and lower extremities along the right sciatic and anterior crural tracts By April 3, 1923, the tumor had filled the pelvis,

FIG 5

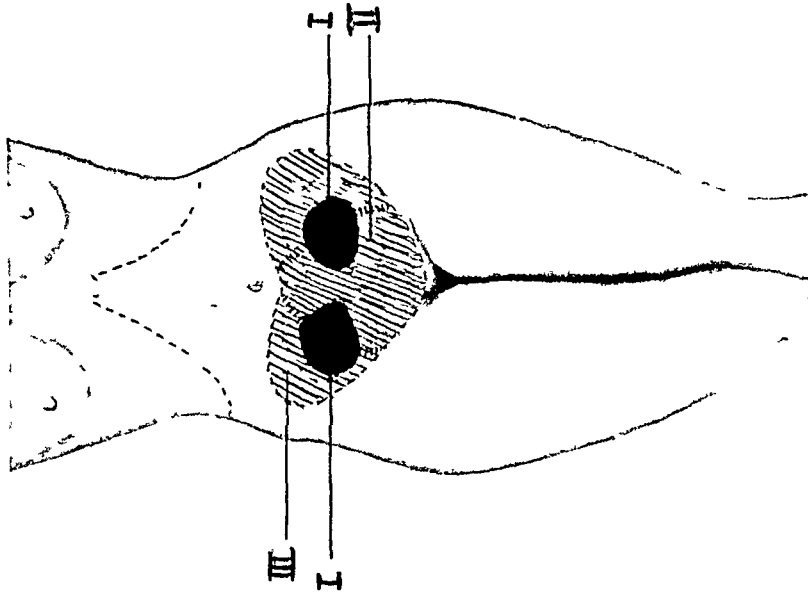


FIG 6

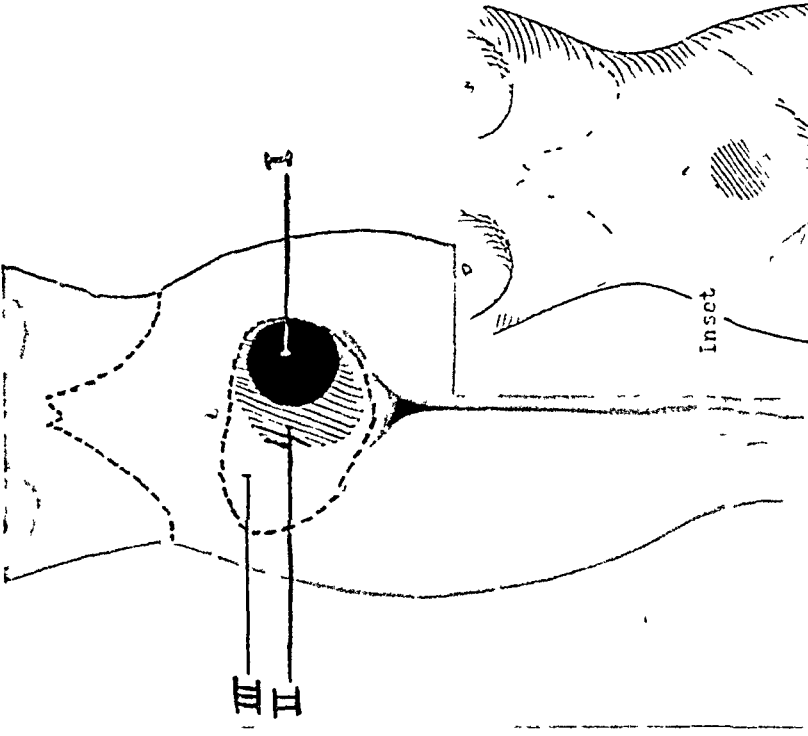


FIG 5—Diagrammatic outline of tumor area to show the two centers or vortices of the greatest circulatory activity before the operation

- I Bilateral centers of loudest murmur and most vigorous pulsation
- II Middle zone of moderate pulsation and bruit
- III Outer zone of least intensity

FIG 6—Diagrammatic outline of contracting area of tumor as felt, April 8, 1921, one year after the ligation of the aorta

- I Contracting center of pulsation and feeble bruit
- II Zone of less active pulsation and inaudible bruit
- III Zone of totally absent pulsation and bruit in radically shrinking sac

Inset—Area of palpable tumor felt June 14, 1921, two months after the preceding observation (14 months after ligation), as a small, fixed, hard, pulseless and silent mass in the infrumbilical region about size of a small mandarin orange. It was now evident that the clot in the sac had consolidated and the aneurysm had ceased to be active.

ANEURYSM OF ABDOMINAL AORTA

projected far above the iliac crest and reached the umbilical level. Roentgenograms showed marked erosion of the bodies of the third and fourth lumbar vertebrae, the promontory of the sacrum and the iliac crests. The diagnosis was then established of a *leaking aneurysm of the abdominal aorta at the bifurcation, involving both common iliacs,*

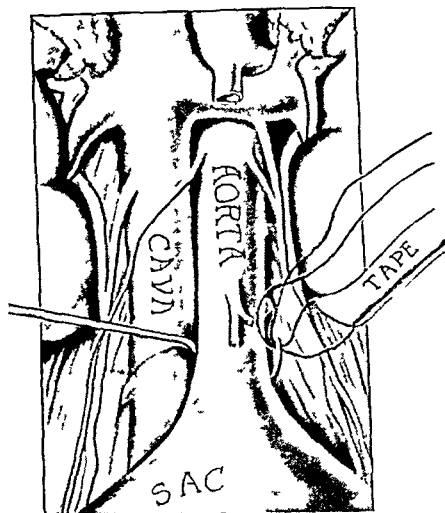


FIG 7—Ligation of the aorta immediately above the sac. One half inch cotton tape led around artery by catgut traction loop and aneurysm needle

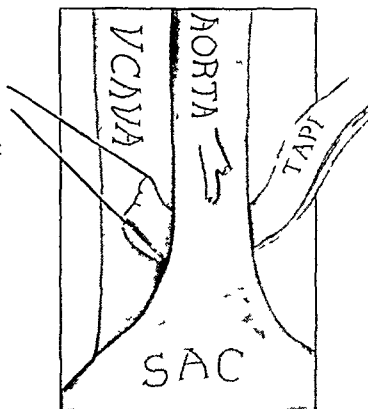


FIG 8—Continuation of Figure 7

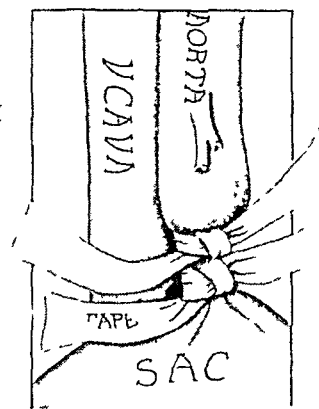


FIG 9—Tape cut in two and applied as double ligature to the artery. Upper tied first, shows first hitch in knot

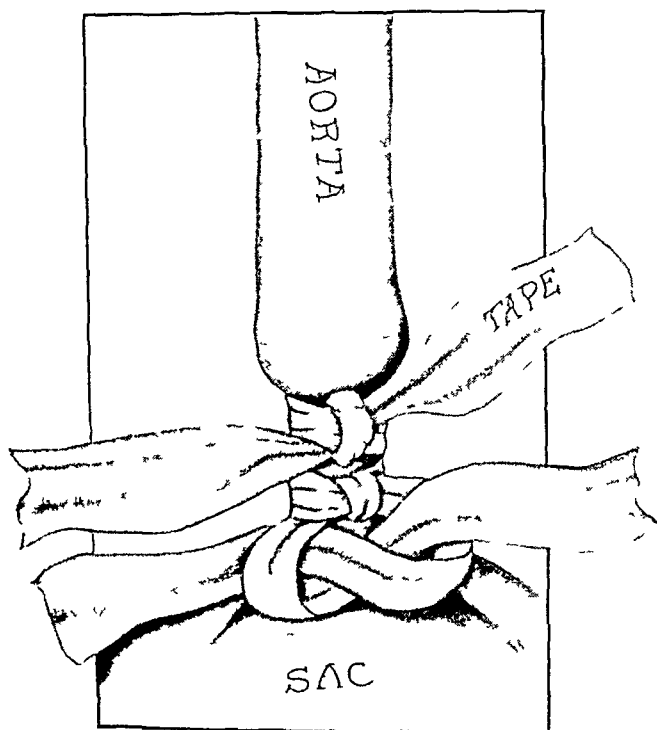


FIG 10—Both ligatures in place. Second knot being tied on lower ligature, second knot already tied in upper ligature

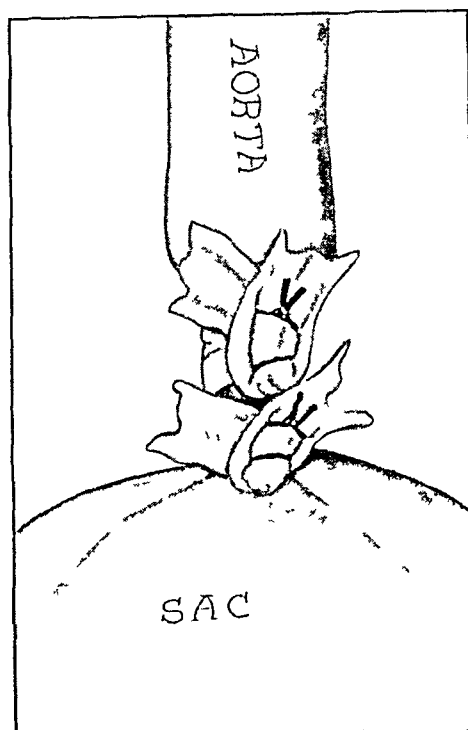


FIG 11—Both knots tied. Knots secured by through and through silk sutures to prevent slipping. The free edges of the tapes were cut short to reduce their bulk

with progressive retroperitoneal extravasation. In view of the great suffering of the patient, and the evidence of a rapidly advancing retroperitoneal extravasation, the ligation of the abdominal aorta above the bifurcation was decided upon and by courtesy of Drs Martin and King, the patient was transferred to Doctor Matas' service



FIG. 12.—Closed sac filled with hard clot exposed in the open pelvis. The grooved director lies in the vorta as it enters the neck of the sac. 1. The right ureter displaced in front of the sac. 2. right iliac artery and underlying vein obliterated and lifted up by expanding sac. 3. left iliac vessels overlapped by extension of sac to left. 4. most prominent bulge of aneurysm at bifurcation, probable seat of original sac before leak began. 5. stiff wire spikes to indicate limits of extravasation when leak occurred.



FIG. 13.—Aneurysmal sac shown empty of clot, filling the right iliac fossa, projecting over the brim of the pelvis, and extending over promontory of sacrum. Deep cavity at the bottom is a diverticulum of the sac projecting into and beyond the sacroiliac notch. The stiff wire spikes indicate the outer boundary of the sac. The grooved director lies in the channel between the vorta and interior of the sac. The vorta is opened and stretched over a glass slide. A folded towel has been placed under the slide and neck of sac in order to bring the vorta into better view.



FIG. 14.—Radiograph shows the outlines of the sac clearly defined after it had been emptied of clot and the clot replaced by a radiopaque medium.

ANEURYSM OF ABDOMINAL AORTA

Operation—April 9, 1923 Doctor Matas and Staff (Drs L H Landry, S Geismar, and A Vidrine, resident intern, Miss Sawyer, chief nurse) Gas-oxygen anesthesia (Dr E E Allgeyer) Operation begun at 9 30 A M and finished at 10 30 A M

Synopsis—Celiotomy in Trendelenburg position Ligation of the abdominal aorta immediately above the sac with two *completely* occluding, one-half inch, cotton tape

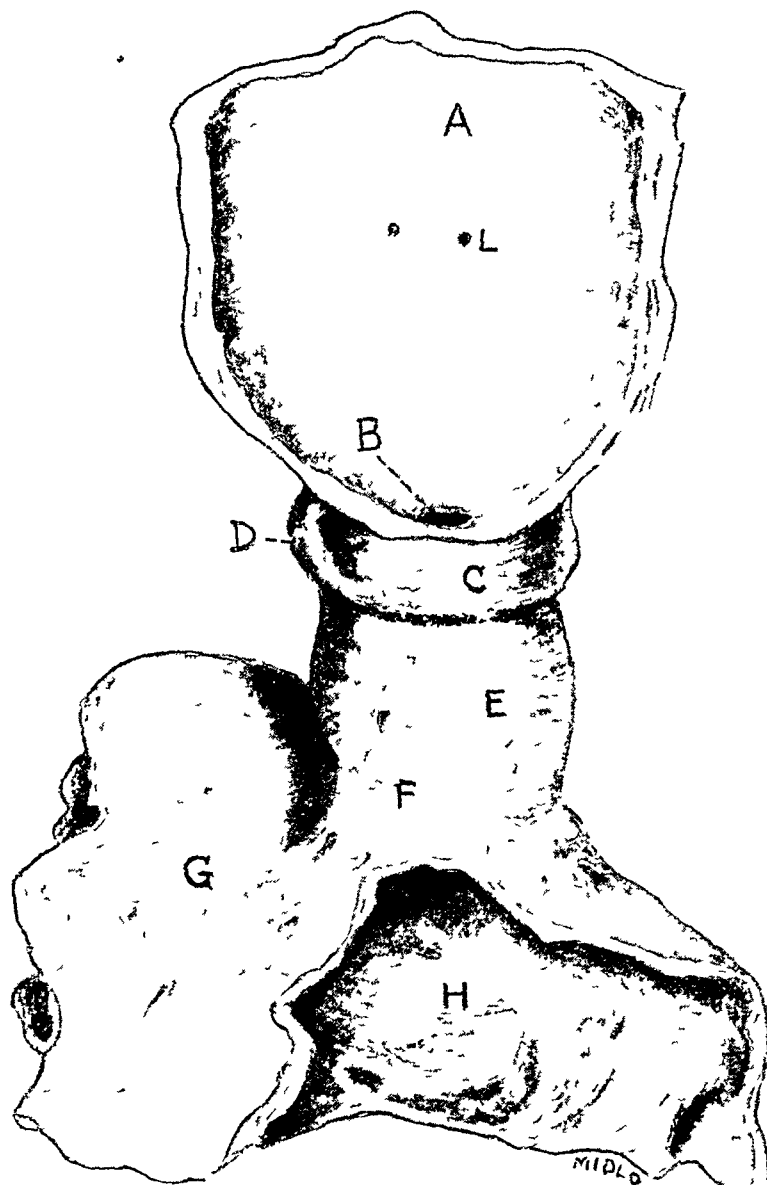


FIG 15—Semidiagrammatic sketch of lower abdominal aorta at the ligation, anterior view. A Aorta cut open as far down as ligature, B, newly formed lumen, C position of cotton tape ligatures, D bulge due to knots, E, pouchlike portion of aorta between ligatures and internal tissue shelf at F, G surface, and H interior of aneurysmal sac which has largely been cut away, L, orifice of fourth lumbar artery

ligatures (sterilized and fat free by preservation in ether) The tapes were placed in juxtaposition, one above the other Upper tape tied first, with first knot secured by silk sutures passed through the knot to prevent slipping Before tying the second knot the effect of the occlusion upon the aneurysm was observed, and it was found that the sac had collapsed and all pulsation had ceased The first knot was tightened with just sufficient force to obtain a complete occlusion without crushing the walls of the artery The second (lower) tape was then tied and the knots secured by sutures in the same way A circular

area of the artery, a little less than one inch in breadth, was thus embraced by the two ligatures. The parietal peritoneum was then sutured over the aorta and the abdomen closed. The appendix, which was long, thick, and beaded with fecal calculi, hung over the aneurysmal sac, and was excised.

Immediate Operative Result—The immediate effect of the ligation was to increase the pulse rate from 121 to 154, and the blood pressure was lowered from 115/85 to 100/70. As the abdomen was closed, the pulse was 160, blood pressure 100/70, respirations rose from 24 to 38. The effect of the ligation on the peripheral circulation was to suppress

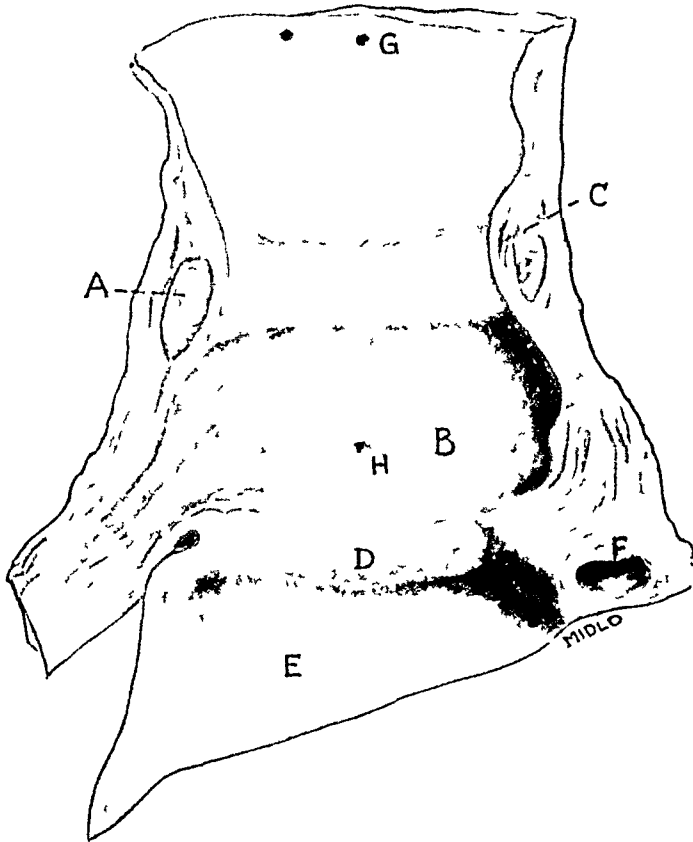


FIG. 16.—Internal view of lower abdominal aorta at the ligation. The anterior wall of the aorta and sac have been cut longitudinally to expose the lumen surface. A, cotton tape ligatures; B, pouch-like portion of aorta between ligature and internal tissue shelf; D, C, areas of calcification; E, wall of aneurysmal sac; F, left common iliac artery; G, orifice of fourth lumbar artery; H, orifice of middle sacral artery.

the femoral and pedal pulses, but the feet retained their sensibility, warmth and living color. Four days after the operation the respirations rose from 40 to 50, coincidentally with the clinical signs of a lobular bronchopneumonia, which appeared in edematous patches in both lungs, accompanied by a profuse mucosanguineous expectoration. The patient continued in a precarious condition, with threatened cardiorespiratory failure, until the ninth day, when relief came with the return of pulsations in the aneurysmal sac and in the femoral arteries in the groin.

Postoperative Course—The postoperative history is one of early relief from pain and rapid reduction in size and activity of the aneurysm, gradual, general improvement in weight and strength under the influence of rest, improved nutrition and specific medication until about April 20, 1924, when signs and symptoms of *progressive tuberculous infection* began to assert themselves in the cervical lymph nodes and in the lungs. Chans

ANEURYSM OF ABDOMINAL AORTA

of caseous tuberculous nodes were twice extirpated, but a rapid infiltration of the lungs with breakdown into cavities, profuse mucopurulent expectoration laden with tubercle bacilli, and "hectic fever" completed the picture of a "galloping phthisis florida," which culminated in a fulminating pulmonary hemorrhage, and death on September 10, 1924. During the year, five months and nine days that the patient survived the ligation of the abdominal aorta, the reduced circulation in the sac, enforced rest, and the extremely low blood pressure that characterized the postoperative period, all combined to promote the deposition of laminated clot and progressive consolidation of the sac.

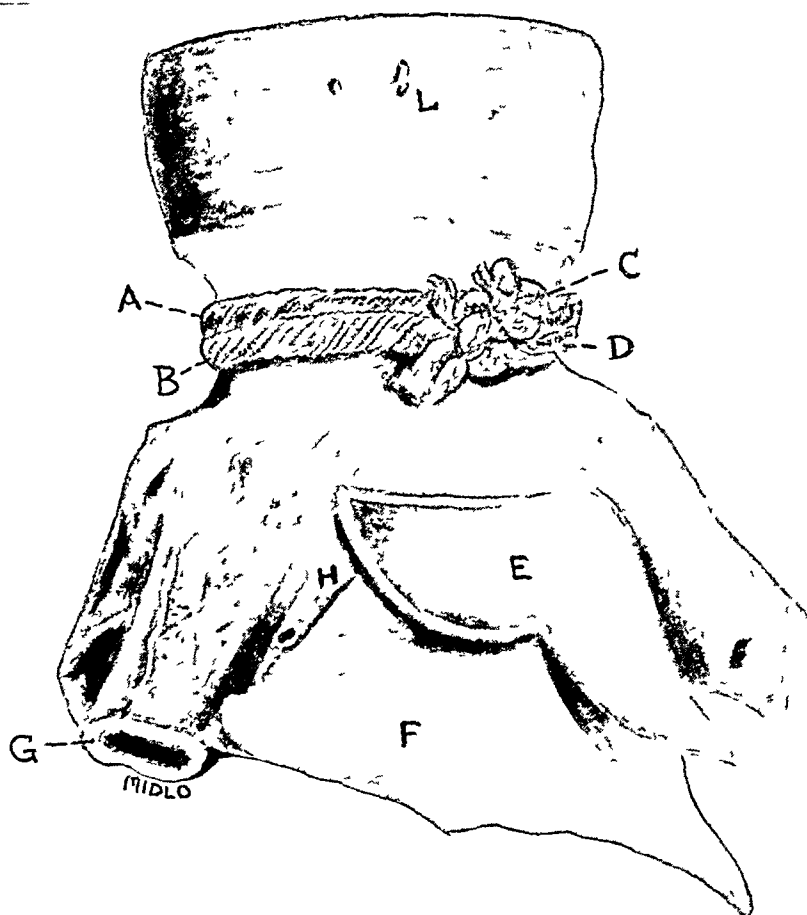


FIG 17—Posterior view of lower abdominal aorta at the ligation. The anterior wall of the aorta and sac have been cut longitudinally. The entire outer aspect of the vessel wall is shown. The tissues covering the outer surface of the ligatures have been dissected away, exposing the two pieces of cotton tape A and B, and their knots, C and D. E, a small portion of the inferior vena cava, F, the upper portion of the aneurysmal sac, G, the left common iliac artery, H, middle sacral artery, L, orifice of fourth lumbar artery.

On April 11, 1924, about one year after the ligation, the aneurysm had contracted fully 60 per cent of its original size, and pulsations could be felt only in small, restricted areas. Three months before the patient's death, the aneurysm had solidified and had lost all of its aneurysmal characters, it had become an inert and symptomless pelvic tumor. The patient died with her aneurysm clinically cured.

REMARKS—Immediately after death every precaution was taken to preserve the body and prepare it for a most searching roentgenologic and anatomic study. The roentgenologic and photographic studies were undertaken at the roentgenologic laboratory of the Charity Hospital, with the valued cooperation of the late Chief, Dr. A. Granger. The histology and photomicrography

FIG 18

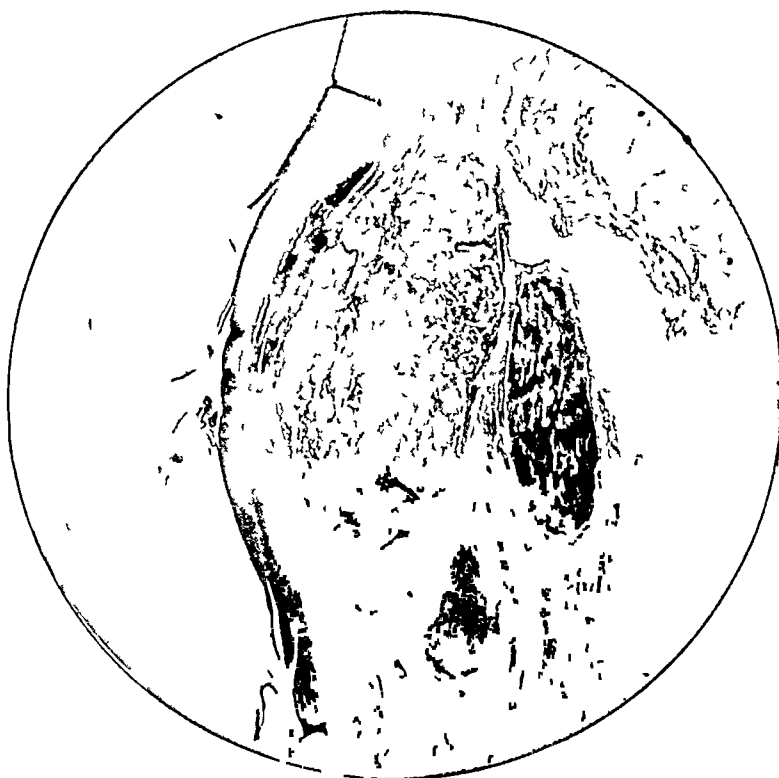


FIG 19

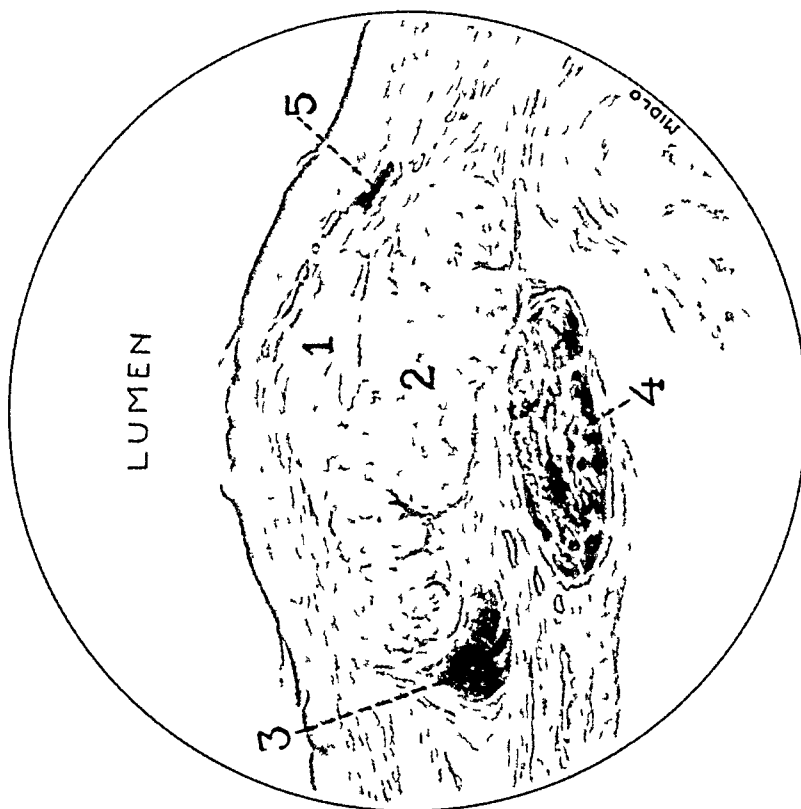


FIG 18 —Photomicrograph of a longitudinal section of abdominal aorta in the region of ligatures (X25) Hematoxylin eosin
 FIG 19 —Drawn from photomicrograph (Fig 18) 1 Necrotic zone probably produced by pressure interference of blood supply 2 cotton type ligatures surrounded by connective tissue and infiltrated with fibrous connective tissue and foreign body giant cells 3 denser zone of connective tissue probably repair process in area of needle passage, 4, small hemolymph node, 5, area of calcification (X25) Hematoxylin eosin

FIG 21

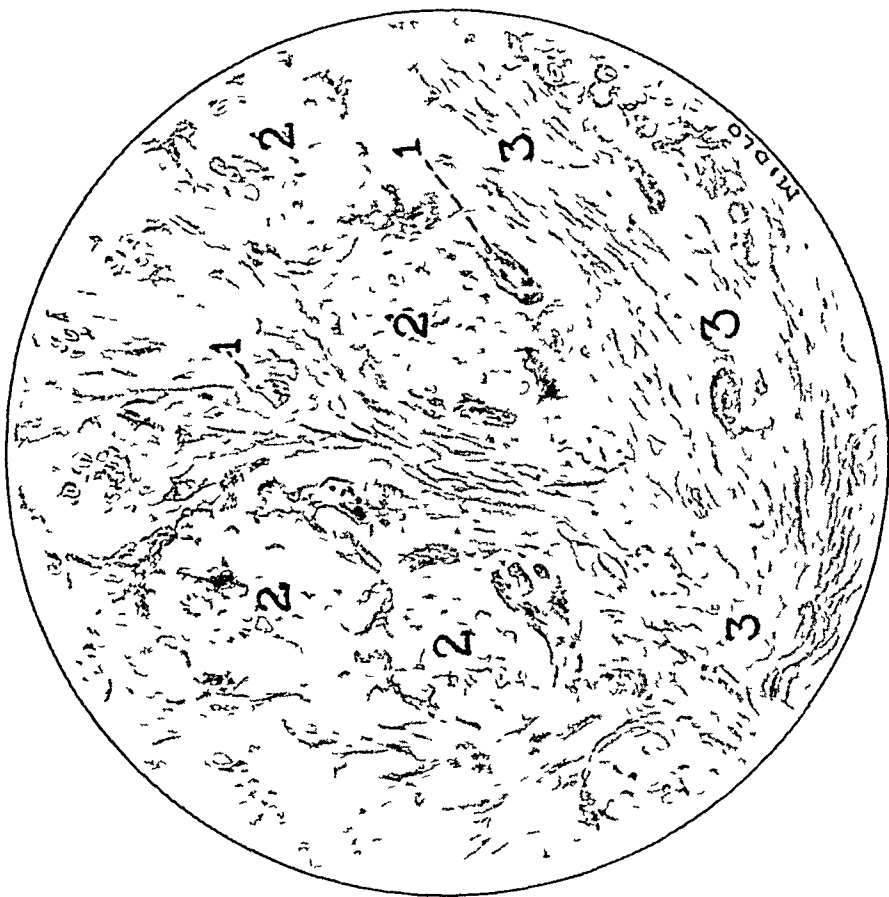


FIG 20

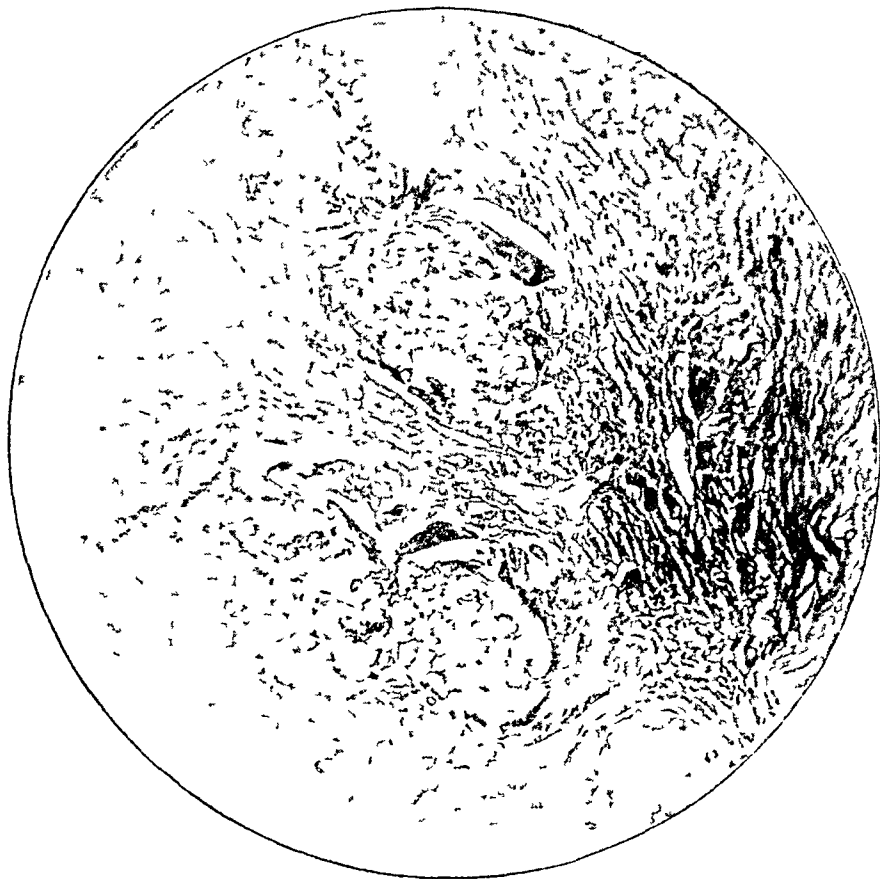


FIG 20 —Photomicrographs of an area of the longitudinal section of the abdominal aorta in the region of ligatures showing some bundles of cotton fibers surrounded by and infiltrated with foreign body giant cells, also, an area of new formed connective tissue, resulting from organization of exudate (X250)
FIG 21 —Drawn from photomicrograph (Fig 20) showing several strands of the cotton tape surrounded by and infiltrated with fibrous connective tissue and foreign body giant cells 1, Giant cells, 2, connective tissue and giant cells in organized exudate (X250)

FIG 23

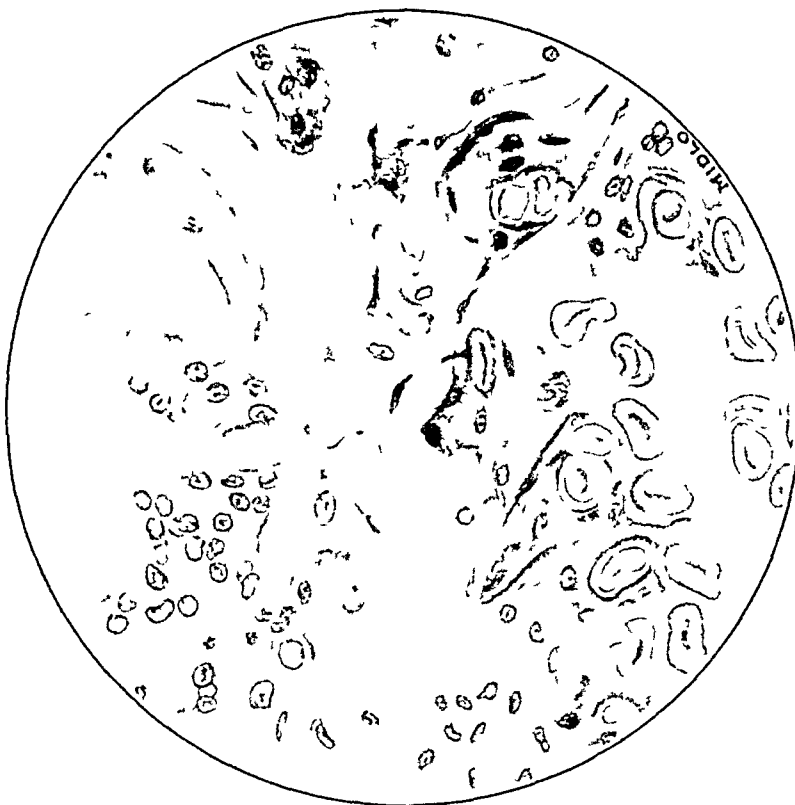


FIG 22



FIG 22—Photomicrograph of a small area of the longitudinal section of abdominal aorta in the region of ligatures showing some fibers of the cotton type, and large foreign body giant cells, some of which have engulfed cotton fibers (X500)
FIG 23—Drawn from photomicrograph showing a number of individual cotton fibers belonging to a strand of the tape used in the ligation, and some of which show engulfed cotton fibers (X500)

were recorded in the laboratory of Professor I Hardesty, of Tulane University by Dr Charles Midlo, his able and painstaking assistant (now assistant Professor of Anatomy, Louisiana State University), to whom I am especially indebted for all the photomicrographs and histologic drawings exhibited in this series (Figs 15 through 22)

The details of the procedure adopted for embalming and injecting the arterial system with radiopaque fluid (a thin colloidal bismuth emulsion) have been described in the author's previous publications, and are the first in which roentgenology has been utilized to visualize (postmortem) the arterial system after a ligation of the abdominal aorta for an aneurysm of this artery. This is, also, probably the first case in which the changes in the ligature and in the tissues of the aorta at the site of ligation have been microscopically studied and photographically recorded.

Among the more salient conclusions that may be drawn from the clinical and postmortem studies of the case are

(1) The patient died 17 months and nine days after the ligation of the abdominal aorta for a leaking (ruptured) syphilitic aneurysm of the abdominal aorta at the bifurcation, including both common iliac arteries

(2) The cause of death was tuberculosis—a cause unrelated to the aneurysm

(3) That the collateral circulation *above and below the aneurysm* was well established before the ligation of the aorta

(4) That the patient had been clinically cured of the aneurysm, and that this had ceased to be an active factor in her invalidism fully three months before her death

(5) The clinical evidence of cure was fully confirmed at the postmortem by the complete consolidation, contraction of sac contents, and beginning organization of the clot

(6) The invalidism and general disabilities, that hospitalized the patient until her death, were caused by the ravages of a disseminated wide-spread pulmonary, lymphatic and joint tuberculosis, which flourished with unusual rapidity and luxuriance in a soil seemingly fertilized by a saturating and malignant luetic infection

(7) The aorta was totally occluded for nine days following the ligation, during which all pulsation ceased and the peripheral pulses in the femoral and pedal arteries were suppressed

(8) During this period of total occlusion, the patient remained in a critical condition from threatened cardiac and pulmonary failure (passive congestion, patchy lobular pneumonia, pulmonary edema), which was only relieved by the yielding of the ligatures sufficiently to allow a small, reduced stream to flow through the ligated segment, thus converting a total *athesia* into a partial, *stenotic* occlusion

(9) The yielding or relaxation of the ligatures was not caused by any slipping of the knots but, as demonstrated at autopsy, by the soaking of the

cotton fibers in the tissue juices, and the permeation and erosion of the fibers by giant foreign body cells

(10) The reduction of the aortic stream to about one-tenth or one-eighth of the caliber of the normal aorta was conducive to the final cure of the aneurysm by favoring a gradual deposition of clot and consolidation of the aneurysmal sac

(11) The anatomic and histologic studies of the aorta at the seat of the ligature showed, conclusively, that the cotton tape ligatures employed in this case (tightened without crushing force) were well tolerated by the tissues and caused no damage to the artery

(12) As shown in Figures 7-11, the two one-half inch cotton tapes remained imbedded and incorporated in the aortic walls as a constricting ring for over 17 months without causing the slightest ulcerative, necrotic or thrombotic changes in the arterial coats and especially the intima which remained well-lined and polished with normal endothelium

(13) This experience shows that a partial occlusion can cure an aneurysm of the terminal aorta slowly, but with greater safety than an immediately total occlusion, without cutting through the artery or causing ulcerative alterations in the intima that might lead to hemorrhage or thrombosis

(14) It would seem that in large and leaking aortic aneurysms, with progressive subperitoneal extravasation, the collateral circulation is well-established. In such cases the immediate total occlusion, which is especially indicated to stop the leaking, may probably be better tolerated than in the earlier and nonleaking aneurysms, in which the collateral circulation has not had time to develop

(15) In view of the fact that sterile cotton tape is so well tolerated by the tissues and is ultimately incorporated by the aorta in the structure of its walls, it would seem unnecessary, and superfluous, to resort to extemporized autogenous fascial strips or to heterogeneous aponeurotic or other membranous strips, kept in stock, when the cotton tape will answer the same purpose with greater simplicity and safety

(16) Judging by the recent experimental evidence and the increasing number of clinical cures of aortic aneurysms by ligation and by suture methods, and the interesting evidence recently furnished by the laboratory, it would seem reasonable to expect that the great desideratum of abdominal aortic surgery, namely, the safe occlusion of the aorta *in any part* of its abdominal and low thoracic course, by gradual methods of occlusion (Owings) will ultimately become as feasible and legitimate in the surgical clinic as in the experimental laboratory

EXPERIMENTAL STUDIES ON THE GRADUAL OCCLUSION OF LARGE ARTERIES*

HERMAN E PEARSE, M D

ROCHESTER, N Y

THE DEPARTMENT OF SURGERY, THE UNIVERSITY OF ROCHESTER, SCHOOL OF MEDICINE AND DENTISTRY ROCHESTER, N Y

THERE is no completely satisfactory method for the gradual occlusion of the great vessels despite repeated attempts to perfect one, for, though many ingenious instruments have been devised, all of them have some drawback. Such a method is desirable in order to treat aneurysm and other lesions of large arteries.

All of the early devices to shut off large arteries used some sort of external compression on the wall. The first of these was with a ligature, but when it was realized that gradual occlusion was necessary, clamps were used that pressed on the vessel indirectly from the outside, often impinging it against a bone. Haberland⁸ shows some of these devices and their method of application. Next, tapes, tubes, clamps or snares were used that encircled the vessel, protruded from the wound and were tightened from the outside. According to Matas,¹² the concept of gradual arterial obliteration was originated late in the eighteenth century. Deschamps⁵ was one of the first to believe "that by gradual obliteration the collateral circulation would be developed sufficiently to diminish the danger of gangrene." He encircled the artery with a wide tape which was held against a flat metallic plate, against which the artery was compressed by tightening the tape with a snare. Dubois⁷ was the first to put this principle into practice by compressing the parent artery of an aneurysm. Assolini¹ devised a spring forceps in which the compression of the artery was regulated with a screw. Subsequently, a great many instruments for arterial compression were made, among which were those of Cooper,³ Doberauer,⁶ Jordan,¹⁰ Keen¹¹ (Fig 1), Riese,²² Smoler,²³ and Stratton.²⁴ It was proposed by Milton¹⁵ that a rubber tube be placed to encircle the vessel and be tightened from the outside (Fig 2). All of these devices had two major disadvantages: that of infection traveling along the sinus from the outside down to the vessel, and that of hemorrhage both from compression atrophy of the vessel wall and from secondary infection about the artery.

Halsted⁹ was the first to overcome the hazard of infection by the introduction of his aluminum band (Fig 3). This was one of the most important contributions to vascular surgery, for it established the concept of aseptic gradual occlusion. In regard to it he says "The notion of gradual compression in the ordinary use of the term was entertained, only to be definitely discarded, because of the seemingly insurmountable difficulty of preserving asepsis. A sinus must form about any instrument leading from the aorta to

* Read before the American Surgical Association, St. Louis, Mo., May 1, 2, 3, 1940.

the an and, sooner or later, such a sinus necessarily becomes infected" Infection predisposes to secondary hemorrhage

Soon after this, Matas¹¹ proposed the use of a heavier aluminum band to be clipped onto arteries to compress them, and thus test the efficiency of the

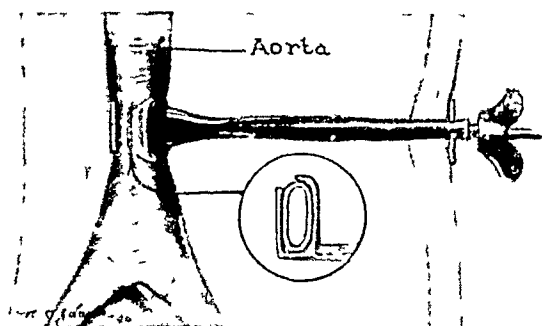


FIG 1—The Koenig¹¹ clamp for gradual arterial occlusion was one of many of the earlier devices employed for this purpose

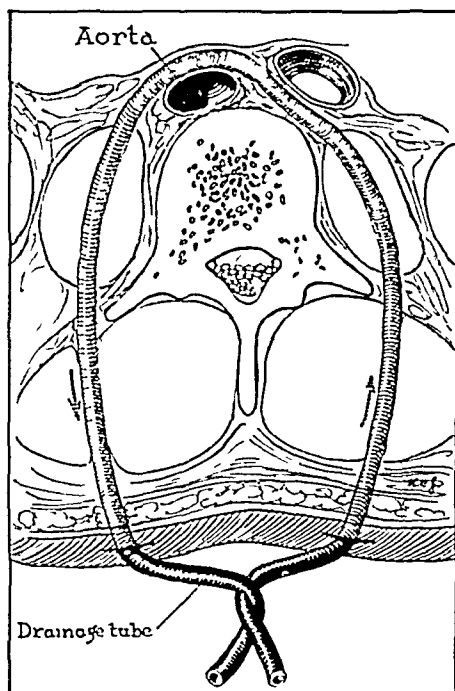


FIG 2—An early method of gradual occlusion of the aorta was suggested by Milton¹⁵ using a rubber tube passing over the vessel and out through incisions on either side of the spine

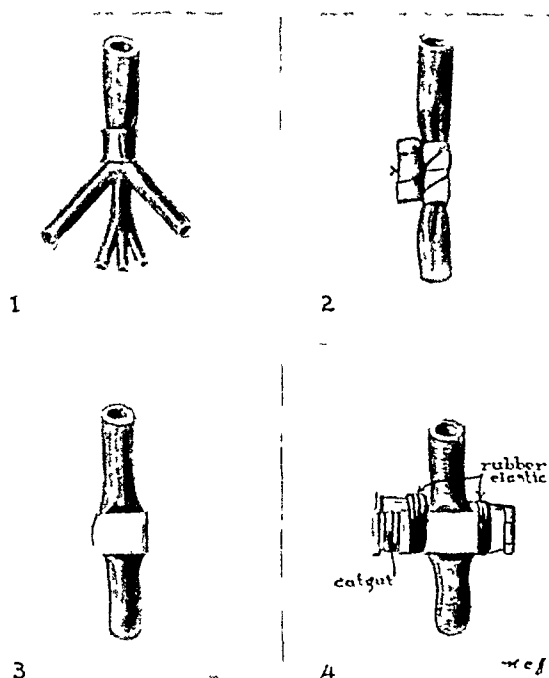


FIG 3—Methods of aseptic gradual arterial occlusion by external compression include (1) The Halsted⁹ band (2) Fascial strips (3) The Matas¹¹ band (4) The Neff¹⁶ clamp These all have the disadvantage of causing pressure atrophy and possible rupture of the vessel

collateral circulation (Fig 3) It was soon used as a means of partial occlusion preliminary to complete obstruction of large arteries Because this band is malleable, it can be applied without a special instrument so is often used to-day instead of the Halsted band

Neff¹⁶ devised an ingenious clamp for gradual, progressive arterial obstruction (Fig 3) He hinged two metallic strips at one end, placing the vessel between them The opposite ends were held apart by strands of plain catgut or decalcified bone, while at the same time elastic bands tended to approximate them As the catgut dissolved, the force of the elastic closed the two metallic strips, compressing and obstructing the artery between them In the experiments reported by Neff in which this clamp was applied to the dog's aorta, hemorrhage or infection occurred in all instances

Finally, ligatures, tapes and tissue bands have been used unsuccessfully to partially obstruct the large arteries Halsted comments on his experiments as follows "Fine silk cut through in two days, coarse silk cut through more slowly, knotted ligatures were found to be unsuitable, for a desired degree of constriction or obliteration could not be accurately obtained nor could the crushing of the arterial wall be invariably avoided Tapes of various materials were tested—of cotton, of chromicized intestinal submucosa, of elastic tissue obtained from the aorta, of aponeurotic white fibrous tissue These tissue bands always relaxed and allowed reestablishment of the lumen" This has been the finding of others¹⁸ who have tried them

Experience has shown that all methods that compress the vessel will eventually cause it to atrophy The expansile pulsation pounding against the compressing device weakens the wall and may even cause rupture with fatal hemorrhage Halsted recognized this danger, for he said "The experimental work on animals had led me to expect that ultimately the metal band must cut through the artery, because in cases observed seven months or less, the wall of the aorta had become atrophied to the thinness of paper and there was no adhesion between the infolded attenuated surfaces" The histologic studies of Reid²⁰ showed this atrophy to be due to loss of elastic and muscular tissues Later, Reid²¹ made the statement that "partial or complete occlusion of a large artery by compression always leads to the death of the vessel wall"

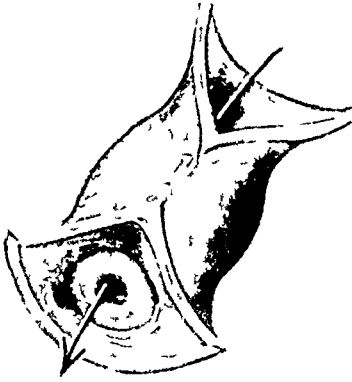
It appears incontrovertible that externally compressing devices are dangerous A consideration of the other alternatives leads to the conception that vessels might be obstructed by internal thrombosis, intrinsic contracture of the wall or extrinsic contracture of scar about the wall These principles have been tested in the following experiments

EXPERIMENTAL STUDIES

All experiments in this field must be interpreted in the light of known differences between the effect of arterial obstruction in animals and in man The dog shows little or no ill effect from abrupt ligation of one or both carotid arteries, while in the human this is followed by cerebral complications in one-third of the cases The same difference in response holds for the ligation of most other arteries Occlusion of the aorta in animals is more comparable to that in the human This is especially true of the thoracic portion, for here sudden ligation invariably causes death in a few hours, the wall is weak and prone to rupture, and the development of collateral circu-

lation is vital. For these reasons the thoracic aorta of animals is the proving ground of methods for use in man. It is assumed in this discussion that a method that is effective on the aorta will be applicable elsewhere.

Methods of Internal Obstruction—Intravascular occlusion was first tried by Reid²¹ with the use of fascial plugs, in order to avoid the atrophy from external compression. He says "For such a method of occlusion there would seem to be no practical demand, for the arteries that commonly need to be occluded in the human being can be occluded by proper ligation. However, some modification of the method, as for example the introduction of a fascial



neg

FIG. 4.—The specimen removed from a dog, who had a spring inserted into the thoracic aorta seven years previously. A major degree of occlusion has persisted since only a small orifice reformed through the original thrombus. The spring steel was intact and showed little evidence of corrosion.

examined several months after operation, a small canal had opened through the thrombus but a major degree of obstruction persisted. This condition is apparently permanent, for it was demonstrated on one dog, observed for seven years after operation, that only this small canal was present (Fig. 4). This animal was active and healthy, being able to run about without apparent fatigue, although the femoral pulses were absent. It was interesting to note, also, that the animal would shiver only in the hind legs in cold weather. These were the only abnormal signs, yet when the specimen was examined it was found that the greater part of the circulation to the lower half of the body was passing through collateral channels.

This method of intravascular obstruction has the disadvantage of technical difficulty in inserting the spring when the vessel is in a deep wound. The device has to be turned parallel to the axis of the artery before it can be completely screwed into place and this maneuver is sometimes hard to accomplish without causing bleeding. To overcome this, a flat spring, such as is used in the mainspring of a clock, was tried. It would curl up in the lumen

ball with a small tube through its center, may be the best way of producing a partial occlusion of the human aorta." Carrel² and others had placed tubes in the vessels only to find that they usually plugged with a thrombus, but this result could be put to use if the rate of thrombotic occlusion was slow enough to permit collateral channels to dilate. Several years ago such a method was proposed¹⁹ which was based upon this principle. In order to avoid the hazard of opening the artery to insert a tube, a coiled tubular spring was introduced through a puncture wound and screwed into the lumen. This caused a gradual closure by thrombosis. In the specimens ex-

to form concentric rings and create a grid across the orifice. This did not work because too much obstruction was caused by the metal and too rapid thrombosis resulted. The flat type of spring produced linear barriers across the lumen rather than forming a tube-shaped structure within it.

Another device tested for this purpose is shown in Figure 5. It consists of a metal cuff which contains 12 sharp projections on its inner wall. This was suggested by Dr. Beverly Raney, who thought that if it was placed snugly

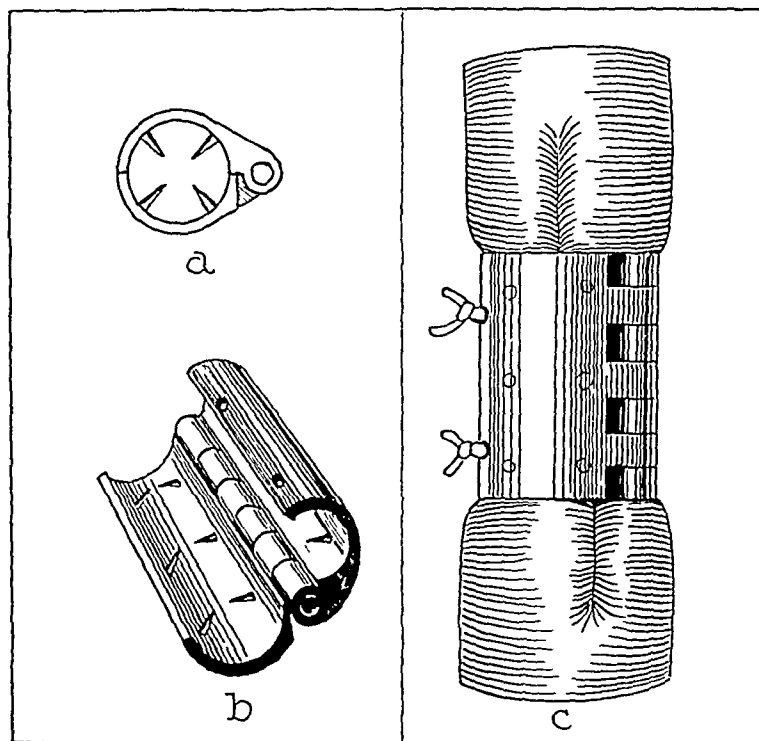


FIG 5—This device contains 12 prongs which were designed to slowly perforate the artery when the clamp was closed over the vessel. The prongs did penetrate the arterial wall but did not do enough damage to cause occlusion by thrombosis.

around the artery the prongs would gradually be forced through the wall and protrude into the lumen, causing thrombus formation. This was a good idea but it did not work, for the penetration of the prongs through the vessel wall was too slow to cause the necessary damage.

Injury to the intima by sclerosing solutions did not cause thrombosis. It was not expected that they would, but they were tried just to make sure that such irritating solutions as sodium morrhuate or 50 per cent glucose would have no effect. A segment of the thoracic aorta of dogs was isolated with rubber-shod clamps, filled with the sclerosing solution, and after one to five minutes the circulation was restored. No obstruction resulted, for it requires not only damage to the intima but also slowing of the stream to produce thrombotic occlusion of a large artery.

Intrinsic Contracture of the Vessel Wall—The first attempt to reduce the caliber of the aorta by constriction of its wall was made by Matas and Allen,¹⁴ using plication sutures. They reported experiments in 151 dogs in which mattress sutures were used to narrow the vessel. This plication was increased

at a second- and third-stage operation until, in some instances, the lumen was nearly obliterated. Reid²¹ performed similar experiments and studied the effect of the sutures on the arterial wall. It was found that relaxation gradually occurred and some restoration of the size of the lumen resulted. In some human cases attempts to suture the diseased wall of the aorta have resulted in hemorrhage.

It is conceivable that sufficient damage to the wall of an artery would result in its eventual contracture with closure of the lumen. This hypothesis was tested by three methods: Injection of irritants into the wall, painting caustics on the outer surface of the wall, and coagulation of the vessel with a diathermy current.

Sclerosing solutions, principally sodium morrhuate, were injected into the wall of the thoracic aorta of dogs, using a very small needle inserted beneath the adventitia. Injection with force causes a ring of solution to infiltrate around the circumference of the artery. The specimens were studied at intervals of from two weeks to three months after injection, and no narrowing of the caliber of the vessel found. In one instance a typical arteriosclerotic plaque occurred on one side of aorta, apparently resulting from the necrosis of the wall at the time of injection.

In another series of experiments, the thoracic aorta of dogs was exposed and a segment denuded of all surrounding tissue (Fig. 6). This part was painted with full strength iodine solution, 35 per cent silver nitrate or 25 per cent aqueous acriflavine. No change occurred in the caliber of the vessel either soon or some time after this treatment. The specimens showed some scarring about the aorta with adhesion of the pleura or lung to the operative site, but the wall of the artery was intact and supple.

The best method of injury to the arterial wall appeared to be with a diathermy current. Twenty experiments were undertaken upon the aorta and carotid arteries by electrocoagulation. The vessel was exposed, denuded, and lifted up by a band of lead foil 3 mm wide (Fig. 6). A coagulating current was passed through this which traversed the two sides of the loop of exposed vessel, gradually coagulating it to a white color. Overcoagulation turns the tissue black and causes it to shrivel to a cord. This can be prevented by using a low milliamperage, allowing some blood to pass through the loop to cool it during coagulation and by careful application of the current. Two machines of Liebel-Flassheim make were used: the "Bovie" and the "Electric Scalpel" models. They were set at low voltage, medium dehydration, and power control of 25 to 30.

The results of these experiments on electrocoagulation of the arterial wall were disappointing. At the time of operation the vessel was constricted to about one-third of its normal size in two places on either side of the contact of the positive electrode. There was no pulse distal to this point but a well-marked thrill was present. The specimens were then examined at intervals of from two to eight weeks after operation. In three experiments overcoagulation occurred with complete occlusion of the lumen by thrombosis.

GRADUAL OCCLUSION OF ARTERIES

This apparently resulted soon after operation. In all others there was a gradual, progressive return of the caliber of the vessel to its normal state. This was usually complete in about a month, after which little or no evidence of injury persisted.

It is seen that in all of the experiments where gradual occlusion was attempted by damage to the vessel wall, the injury was insufficient to cause

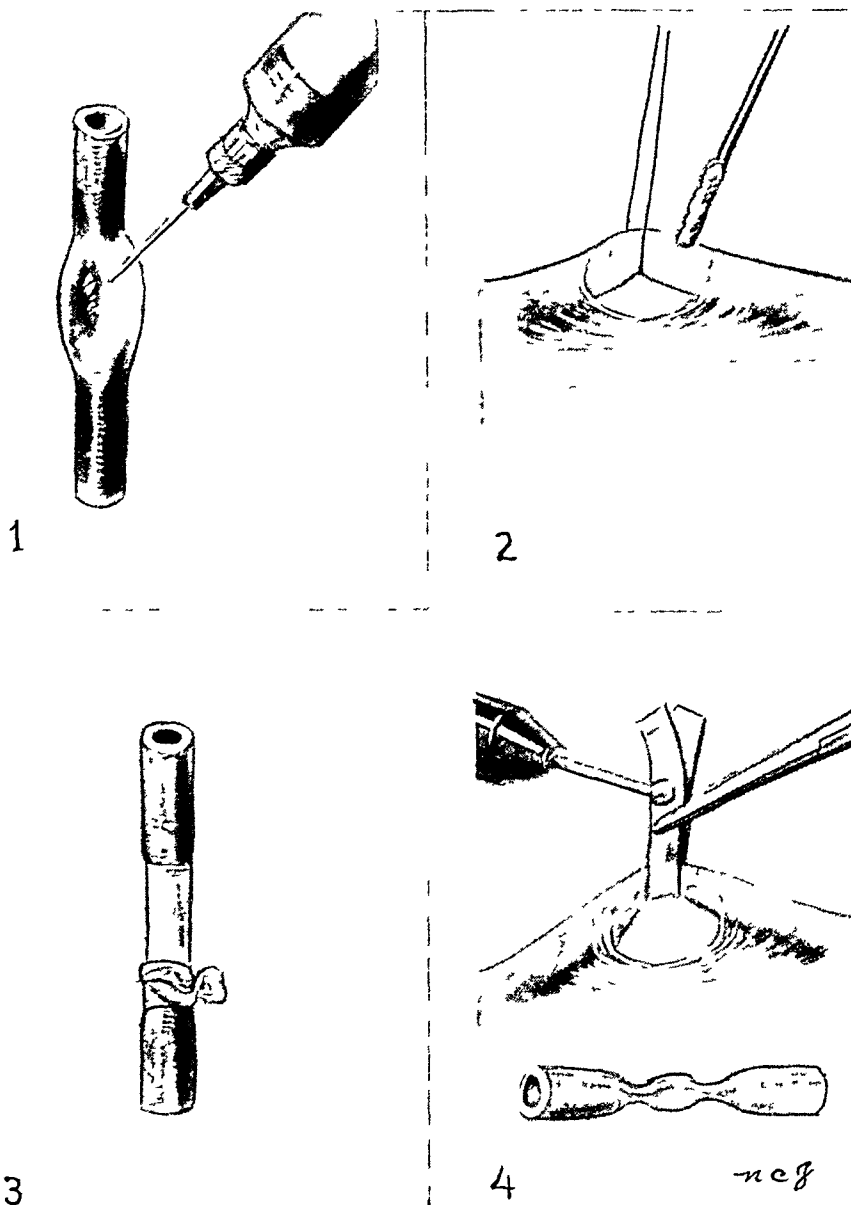


FIG 6—Methods of injury to the arterial wall in an attempt to induce spontaneous closure from contracture included (1) Injection of irritants into the wall (2) Painting irritants onto the wall (3) Wrapping cellophane about the vessel (4) Slow coagulation of the wall with diathermy

permanent constriction of the artery. In fact, that produced at operation eventually relaxed and allowed restoration of the normal caliber. In view of this, it is probable that the reparative capacity of the artery is great enough to correct a sublethal damage, so the attempt to produce gradual progressive occlusion by this means is unsatisfactory.

Occlusion by Extravascular Contracture—Theoretically, an artery could be shut off by the contracture of a large amount of scar tissue about its wall

The first attempt to do this was with strips of fascia¹⁸ which were wrapped around the aorta, making a concentric ring of fibrous tissue about it. This fascia gradually relaxed and eventually absorbed so that no evidence of obstruction existed after two or three months.

Cutler¹ has used acriflavine to cause fibrotic occlusion of the bronchus. This substance causes fibroplasia in tissue, so might be used to constrict arteries with scar tissue. Acriflavine, in a 25 per cent aqueous solution freshly prepared before each experiment, was injected in the tissues about the thoracic aorta of dogs. It was infiltrated around the vessel for a distance of about one inch along its course. The specimens were examined at intervals of one, two and three months and no contracture found that was sufficient to constrict the aorta. Only six experiments were undertaken, so it may be worth while testing this compound more thoroughly. If greater periarterial infiltration could be accomplished on repeated applications made, it might produce more effect.

Silica is known to produce extensive scarring in pulmonary tissue causing pneumoconiosis. How much fibroplasia it causes in other tissues is not so well known. Recently, it was decided to try placing silica, in finely divided particles, into the tissues about the aorta in an effort to cause extensive scarring around the vessel. There are insufficient data available at present to judge the results of these experiments, which are being continued.

Page¹⁷ found that cellophane wrapped loosely about the kidney caused an excessive reaction in the tissues, constricting the kidney and causing hypertension in dogs. It is conceivable that if the reaction from cellophane was great enough to contract a kidney it would be sufficient to squeeze down the caliber of a large artery.

Twenty-four experiments were undertaken by wrapping cellophane about the aorta or carotids of the dog. Ordinary DuPont cellophane No. 300 P T was used that was soaked in alcohol or mercury oxycyanide solution at least for 12 hours prior to operation. It was folded into a strip four layers thick and loosely wrapped about the vessel three times. The ends were tied to hold them in place or a silk ligature was placed around the ends. Every effort was made to avoid external compression on the artery but in spite of this the cellophane was tight enough to cause rupture of the aorta in one animal*. Another dog died of a pulmonary infection soon after operation. The remainder were satisfactory for evaluation of the method.

Cellophane was found to be an extreme tissue irritant, for, with but two exceptions, an extensive change occurred around it. This consisted of an intense reaction with either purulent or gelatinous fluid in the center about which the tissue contained many phagocytic, mononuclear cells interspersed among fibrous tissue. This fibrocollagenous layer became partly hyalinized. This process causes a steady progressive constriction of the vessel and an eventual obliteration of the lumen in some instances. Figure 7 shows, by means of latex injection casts, how the caliber of the abdominal aorta was

* In a subsequent series of experiments two other dogs have died of rupture of the thoracic aorta.

diminished by the tissue reaction from cellophane wrapped about it. As the process continues there comes a time when the intima is involved and destroyed, shutting off the vessel completely (Fig 8)

This is the first time that gradual obstruction of the aorta has been deliberately produced by perivascular irritation. The only drawback to the method is the intensity of the reaction caused by the cellophane. It makes one hesitate to use it in patients, yet apparently a very extensive irritation is necessary to shut off these large arteries since lesser degrees of damage have no effect. Perhaps the amount of cellophane applied could be reduced to a point where it was just sufficient to cause occlusion but not enough to create such an extensive reaction in the surrounding tissues. This is being tried.

The importance of these observations lies in the demonstration that gradual occlusion of the dog's aorta can be produced by a fibroplastic reaction in and about the vessel wall, thus illustrating the feasibility of such a method.

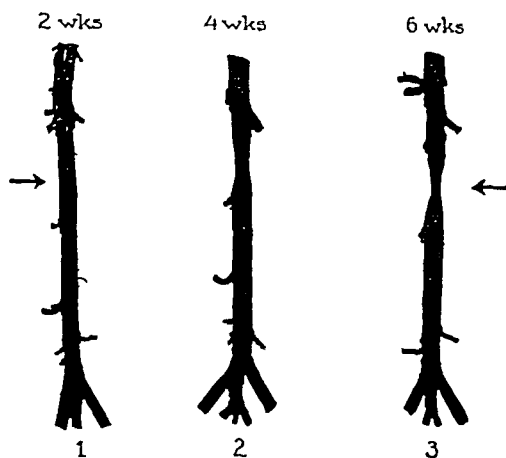


FIG 7—Gradual progressive constriction of the dog's abdominal aorta by contraction from cellophane irritation is demonstrated by these latex injection casts of the vessel. The arrows point to the level of injury.

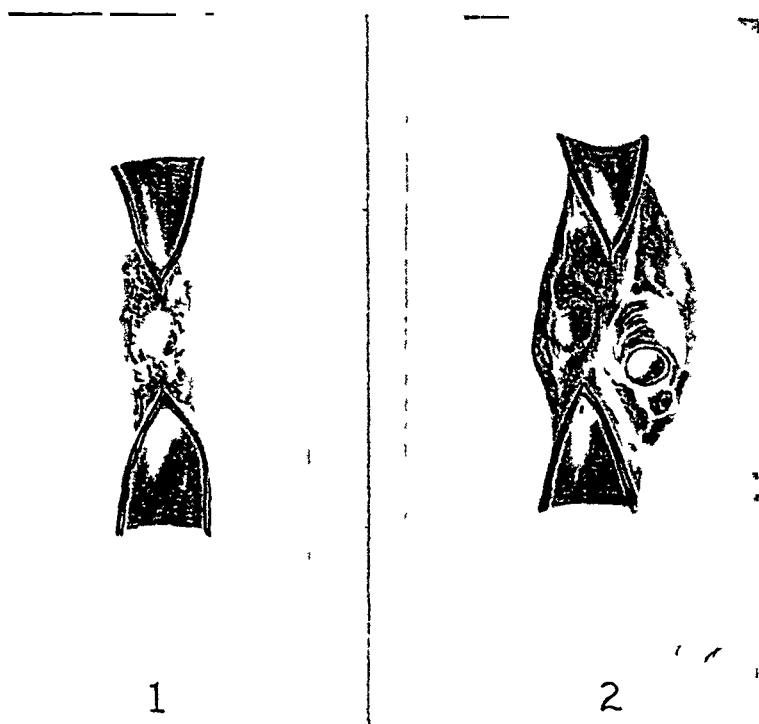


FIG 8—Two specimens of complete occlusion of the dog's aorta by cellophane wrapped loosely about the vessel. The first one has a central crater which contained fragments of cellophane while in the second the cellophane retained its circular form but migrated to one side of the artery.

SUMMARY—During the last century many attempts were made to produce gradual progressive occlusion of the aorta and other large arteries by means

of bands, clamps or ligatures which compressed the vessel. All experience has shown that the force of the pulse pounding against the compressing device will weaken and rupture the arterial wall. All methods that depend upon external compression are dangerous.

Theoretically, there are at least three other methods by which large arteries can be gradually obstructed. By internal occlusion with thrombosis, by intrinsic contracture of the vessel wall after its injury, and by extrinsic contracture of scar tissues around the artery. These have been tested experimentally.

About 12 years ago, a method was reported for closing the thoracic aorta of dogs by thrombosis caused by a spring screwed into its lumen. Continued observation of these animals, one of them for seven years, reveals the persistence of a major degree of obstruction. The particular virtue of the spring is the tenacity with which it holds the thrombus by the multiple coils within the lumen. This not only prevents embolism but also gives a more permanent occlusion. The disadvantage of the spring is the difficulty of inserting it into the vessel in a deep wound, but thus far, no better method of intravascular closure has been found.

Intrinsic contracture was attempted by injury from iodine, silver nitrate, sodium morrhuate or acriflavine painted on the arterial wall or injected into it. This caused no narrowing of the vessel. Diathermy coagulation resulted in temporary constriction but eventual restoration of the lumen to a normal caliber. There is apparently too little damage produced by these means to cause occlusion or even permanent constriction of the aorta.

Extrinsic contracture of the perivascular structures was first attempted by the use of large amounts of fascia but this relaxed rather than contracted. Acriflavine and silica have been tried without effect as yet.

A striking result followed the use of cellophane wrapped loosely about large arteries. An intense perivascular irritation was produced by the cellophane, with first constriction of the vessel and then invasion and destruction of the intima resulting in complete closure. This occurred even with the aorta. It is the first time that complete occlusion has been produced by the extravascular contracture.

CONCLUSION

Closure of the aorta both by intravascular thrombosis and by extravascular irritation has been demonstrated. It remains to perfect the methods by which this is done, for they can, in all probability, be improved.

BIBLIOGRAPHY

- ¹ Assolini, Paul. *Manuale di Chirurgia*. Napoli, 1819.
- ² Carrel, A. On the Experimental Surgery of the Thoracic Aorta and the Heart. *ANNALS OF SURGERY*, 52, 83, 1910.
Idem. Permanent Intubation of the Thoracic Aorta. *Jour Exper Med*, 16, 17, 1912.
- ³ Cooper, Sir Astley. *Cooper and Travers's Surgical Essays*, 1, 83, 1817.
- ⁴ Cutler, E. C., and Wood, C. B. Studies on Endobronchial Occlusion. *Surg, Gynec and Obstet*, 59, 501, 1934.

- ⁵ Deschamps, J F L Observations et reflexions sur la ligature des principales arteres blesees, et particulierement sur l'anevrisme de l'artere poplitee 2nd ed, Paris, 1797
- ⁶ Doberauer Die Unterbindung Grosser Gefassstamme mit Hilfe der Allmahlichen Zuzchnurung Verhandl d Deutsch Ges f Chir, 122, 1908
- ⁷ Dubois, Baron Antoine (work described by Duret, F J J) Dissertation sur la compression immediate de l'artere dans l'operation de l'anevrisme Paris, 1810
- ⁸ Haberland, H F O Die Entwicklung und Fortschritte der Gefasschirurgie Ergeb d Chir u Orth, 15, 257, 1922
- ⁹ Halsted, W S The Partial Occlusion of Blood Vessels, Especially of the Abdominal Aorta Johns Hopkins Hosp Bull, 16, 346, 1905
Idem Partial Occlusion of the Thoracic and Abdominal Aorta by Bands of Fresh Aorta and of Fascia Lata Trans Am Surg Assn, 31, 218, 1913
Idem Partial, Progressive and Complete Occlusion of the Aorta and Other Large Arteries in the Dog by Means of the Metal Band Jour Exper Med, 11, 375, 1909
- ¹⁰ Jordan, Max Zur Ligatur der Carotis communis Verhandl d Deutsch Ges f Chir, 83, 1907
- ¹¹ Keen, W W A Case of Ligature of the Abdominal Aorta Just Below the Diaphragm, the Patient Surviving for 48 Days, with a Proposed Instrument for the Treatment of Aneurysms of the Abdominal Aorta by Temporary Compression Am Jour Med Sci, 120, 251, 1900
- ¹² Matas, R Personal communication
- ¹³ Matas, R Occlusion of Large Surgical Arteries with Removable Metallic Bands to Test the Efficiency of the Collateral Circulation J A M A, 56, 253, 1911
- ¹⁴ Matas, R, and Allen, C W Conclusions Drawn from an Experimental Investigation into the Practicality of Reducing the Caliber of the Thoracic Aorta by a Method of Plication or Infolding of Its Walls by Means of a Lateral Parietal Suture Applied in One or More Stages Trans Am Surg Assn, 31, 196, 1913
- ¹⁵ Milton, H Ligature of the Abdominal Aorta for Ruptured Aneurysm of That Vessel, Death Lancet, 1, 85, 1891
- ¹⁶ Neff, J M A Method for Gradual Automatic Occlusion of the Large Blood Vessels at One Operation J A M A, 57, 700, 1911
- ¹⁷ Page, I H The Production of Persistent Arterial Hypertension by Cellophane Perinephritis J A M A, 113, 2046, 1939
- ¹⁸ Pearse, H E The Impracticability of Using Fascia for the Gradual Occlusion of Large Arteries Am Jour Surg, 16, 242, 1932
- ¹⁹ Pearse, H E A Method for the Gradual Occlusion of the Aorta Surg, Gynec and Obstet, 46, 411, 1928
- ²⁰ Reid, M R Partial Occlusion of the Aorta with the Metallic Band Observations on Blood Pressure and Changes in the Arterial Wall Jour Exper Med, 24, 287, 1916
- ²¹ Reid, M R Partial Occlusion of the Aorta with Silk Sutures and Complete Occlusion with Fascial Plugs, the Effect of Ligatures on the Arterial Wall Jour Exper Med, 40, 203, 1924
- ²² Riese, H Uber die temporare Ligatur der Grosser Gefassstamme mit besonderer Berucksichtigung der Constriction der Carotis als Voroperation zur Oberkieferresection Deutsch Med Wchnschr, 22, 67, 1896
- ²³ Smoler, H Zur Drasselung Grosser Gefassstamme Verhandl d Deutsch Ges f Chir, 249, 1911
- ²⁴ Stratton, R T The Gradual Surgical Occlusion of Large Arteries, Its Relative Advantages Together with an Experimental Inquiry as to Its Feasibility ANNALS OF SURGERY, 38, 256, 1903

DISCUSSION—DR EMILE HOLMAN (San Francisco, Calif) We are, indeed, grateful to Doctor Peaise for giving us another method of treating large arteries when we are confronted with the necessity of occluding them

I am reminded of Van Allen's suggestion that patients might be prepared for lobectomy by wrapping the affected lung in cellophane, waiting for fibrous contraction to occur, and then, subsequently, performing a lobectomy. This was done in experimental animals with great success, indicating that there is a very definite stimulating effect of cellophane upon the production of fibrous tissue.

I can visualize one site where such an irritating substance might be used to advantage. I recently operated upon a young child with a patent ductus arteriosus. There was definite improvement, as shown by a rise in diastolic pressure and a decrease in dyspnea. However, a thrill occurred two days after operation which persists to the present time, and I am convinced that there has been partial restoration of the patent ductus. Is it not possible that, at this site, one could use some such gradual occluding agent?

With reference to the ligation of large arteries in continuity, attempt has been made by operators to prevent the erosion of the artery by using larger and larger occluding ligatures. However, they all have the inherent danger of the fact that this ligature is applied at a fixed point and that the distending force of pulsation is directed at this point with each beat of the heart, with gradual rupture of the tissue and rupture of the vessel. When we divide a large artery, as, for example, the abdominal aorta in the dog, there is a retraction of 3.8 cm., and separation of the divided ends due to elasticity.

Following division of the artery, there is no fixed point. The force of each pulsation is used up in the lateral expansion and in the lengthening of this proximal segment, so that there is no tendency for rupture of the tissues at the point of ligation. I think we should endeavor, in every instance, to divide a large artery between ligatures rather than to ligate it in continuity.

DR. FREDERICK L. REICHLERT (San Francisco, Calif.) I simply wanted to ask Doctor Pearse if the work of Doctor Van Allen, published some five or six years ago, in which he demonstrated the use of rubber, silk, and, I think, cellophane around large arteries, was not much the same as he has done.

DR. RUDOLPH MATAS (New Orleans, La.) In dealing with the gradual occlusion of the aorta and its primary branches, Doctor Pearse has brought up one of the most important problems in vascular surgery. He has reviewed all the important evidence on this subject very graphically and instructively. Unfortunately, and despite the great study, scientific ingenuity and experimental research that has been given to this problem, a safe, practical method of gradual occlusion of the human aorta has remained an unfulfilled desideratum.

In 1910, a great wave of experimental activity in the surgery of the vascular system had spread all over the world in consequence of the new impetus given to blood vessel techniques by Carrel's improved method of suture. At the same time, the increasing incidence of aortic aneurysms as they were being disclosed by roentgenologic examinations intensified the search for methods of cure and relief by an improved surgery. The chief objectives of the experimental laboratories were the thoracic and abdominal aortas, in which the failure of the immediate, total ligature had led to a better prospect by the methods of gradual occlusion.

It was in this way that, in 1910, and contemporaneously with many other investigators (Haecker, Carrel, Halsted, Guleke, Jager, Lawen and Sievers, Schuppelmann, *et al.*), I undertook a long series of experiments in association with my friend and most valued assistant, the late Dr. Carrol W. Allen*.

* Matas and Allen. Trans. Am. Surg. Assn., 31, 195-217, 1913. *Idem*. ANNALS OF SURGERY, 58, 304-319, September, 1913.

in which we aimed at the gradual occlusion of the thoracic aorta (below the left subclavian) by a series of plications, or infoldings, of the aortic walls which were turned into the lumen of the aorta, thereby reducing its lumen in proportion. The plan was to undertake the infolding at intervals—in about three stages. In the last stage, the infoldings filled the artery completely and transformed it into a solid cylinder which was to be cut through and the ends closed with tight ligatures. In this way we hoped to repeat, in the thorax, what Doctor Allen had already accomplished in the abdomen by the gradual obliteration of the aorta below the renals. This he had done in two or three stages with our modification of the Halsted aluminum bands, following which the aorta was divided through the obliterated segment, between sutures. A number of dogs died from premature cutting of the aortic walls by the bands, but the occlusion succeeded often enough to prove that the complete division of the aorta below the renals could be made effective by gradual occlusion, provided the bands were removed in time to anticipate the perforation and fatal hemorrhage, which occurred more often after the seventh or tenth day. The dangers of the metallic compression led me to try the method of occlusion by plicating the thoracic aorta which, with Doctor Allen's able assistance, I tried, at irregular intervals, for two and one-half years (1910-1913), during which the operation was performed on 151 dogs. Seventy dogs survived the first plication, 73 the second, and 11 reached the third or obliterative plication. But it was found that when the infolded walls filled the lumen of the aorta, the force of the systolic wave stretched a passage for a narrow blood stream beyond the seat of the obstruction. While no dogs survived the third plication, and they did not live long enough to permit a complete *dry* section of the plaited segment, the experiments demonstrated the capacity of the heart and collateral vessels to adjust themselves to an extreme degree of aortic stenosis which would have been fatal if the artery had been suddenly closed by a total ligature.

As the defects and failures of all previous methods of gradual occlusion have been fully brought out by Doctor Pearse, I will not consume more time with further commentaries on past or historic procedures. I am glad, however, to avail myself of this opportunity to submit to your consideration a new and unpublished method of gradual occlusion of the aorta, both abdominal and thoracic (outside of the arch), which promises to deliver the long sought procedure of a gradual and safe aortic occlusion, at least as this has been found effective in dogs and, now, holds a good prospect that it will be found equally feasible in man. For this privilege, I am indebted to Dr. James C. Owings, a young and capable experimenter—assistant to Dr. Harvey B. Stone in the Surgical Hunterian Laboratory at Baltimore—who has just been mentioned by Doctor Stone in connection with his experiments with heparin.

Through Doctor Owings' personal letters, I have learned of his successful efforts to obtain a gradual but complete occlusion of the abdominal and thoracic aortas, in practically any part of their course, by means of a rubber band which is made to conform to the shape of an hour-glass. The band, acting as a ligature, is narrowed progressively in three operations at intervals of about three weeks each. Wide stationer's rubber bands for the preliminary compression were chosen because they give with the pulsation of the vessel, to a certain extent, and are, therefore, less likely to cut through than metallic bands. The rubber band is plicated into the shape of an hour-glass so that there is no abrupt change in the caliber of the vessel, thereby eliminating the sharp edge against which the vessel wall would otherwise be constantly butting.

It has been necessary to apply three of these bands at three successive operations at three weeks' intervals, before sufficient collateral circulation has

been developed to make ligation possible. When the third stage is reached the vessel is doubly ligated with braided silk and the intervening segment is thoroughly crushed with Kelly forceps, to promote thrombosis and fibrosis. The ligatures are separated from each other by about 1.5 cm, after which the crushed segment is cut between ligatures. On April 1, 1940, Doctor Owings wrote that he had four dogs ready for this final step. One of these had been tied off for nearly a year and the others about seven months. The rubber bands are applied at three-week intervals, one below the other, or, occasionally, one over top of the other. This is necessary to produce sufficient collateral circulation because the yield of the ligature plus the atrophy of the aortic wall is enough to reestablish the pressure below the ligature within about three weeks and, if it is not again compressed at least twice, the animals die, from insufficient circulation to the kidneys and liver, when the final occlusion is made.

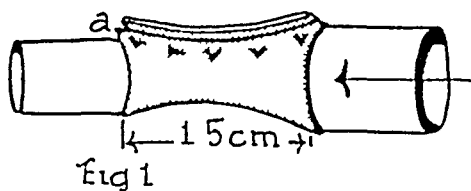


Fig 1

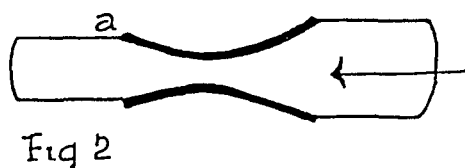


Fig 2



Fig 3 (a)



Fig 3 (b)

FIG 1—(a) Cut edges of rubber. One edge is sometimes left long and folded over the short edge to make it smooth.

A rubber band is placed around the aorta and fixed in position with mattress sutures. Tension is judged by a flabby vessel below with no pulsation and only a faint thrill to be felt.

FIG 2—Longitudinal section to show what a guess it is to estimate the degree of constriction. Note that segment above band is much larger than below. A band is placed just above an intercostal vessel to keep it from slipping down.

FIG 3—(a) Aorta tied and segment between ties crushed with a Kelly clamp to induce thrombosis and fibrosis. Note that upper and lower segments at this stage are nearly the same caliber because there is very little tension in either of them. The ties are of heavy braided silk. It is usually necessary to apply three bands, either one immediately below the other or one over top of the other at three or four week intervals before sufficient collateral circulation can be developed, because tension returns by atrophy of the vessel wall and relaxation of the bands.

FIG 3—(b) Final stage. Showing the crushed and obliterated segment of aorta divided.

In dealing with the thoracic aorta the rubber bands were applied to the descending portion below the arch. He has made no attempt to obliterate the vessel proximal to the arch. The surgical approach has always been transpleurally by an anterior thoracotomy.

On May 21, 1940 (after the meeting of the American Surgical Association at St. Louis) Doctor Owings wrote: "Since my last letter I have cut across the aorta below the point of constriction, ligating the two ends with ordinary black silk and allowing them to retract. All three animals have done very well. In fact, they were up and eating within a few hours after the operation."

"I am going to make some studies on kidney function and try to get roentgenograms of the collateral circulation before the animals are sacrificed, and hope to report the work in further detail before the Southern Surgical Association, next fall."

In order to give a still further conception of Doctor Owings' procedure he has, obligingly, made four diagrammatic sketches which I am reproducing with their appended legends (Figs. 1, 2 and 3a and b).

No one who is familiar with this type of experimental work can fail to be

impressed with the simplicity and soundness of Doctor Owings' procedure and the very extensive field of surgical application which it suggests, since it is applicable to the whole extent of the aorta from the arch to the bifurcation

DR HERMAN E PEARSE (Rochester, N Y, closing) Several questions were asked me concerning the cellophane that was wrapped around the vessels. It was ordinary DuPont cellophane, No 300 P T, soaked in alcohol or mercury oxycyanide, folded to two or four thicknesses, making a strip about 1 cm wide and wrapped loosely twice or three times around the vessels. The ends were tied or were sutured with silk, to hold them from slipping.

As to Doctor Reichert's question, I must confess my ignorance. I know of some of Doctor Van Allen's publications, but I did not believe that he had used cellophane.

It is possible to divide the thoracic aorta completely. I have done it after thrombosis with the spring. The reaction of the dog's thoracic aorta is exactly comparable to that of many human arteries, and I believe this should always be kept in mind in experimental work on the subject.

DR FRANK LAHEY (Boston, Mass) How does cellophane cause this reaction?

DOCTOR PEARSE I do not know. It is a terrific reaction, long-continued and persistent but not associated with ordinary inflammation. There are very few polymorphonuclear leukocytes in the tissue. There are many large phagocytic cells often containing fragments of cellophane, which would lead one to believe that it is a foreign body reaction.

THE PREVENTION OF ISCHEMIC GANGRENE FOLLOWING SURGICAL OPERATIONS UPON THE MAJOR PERIPHERAL ARTERIES BY CHEMICAL SECTION OF THE CERVICODORSAL AND LUMBAR SYMPATHETICS*

MIMS GAGE, M D ,

AND

ALTON OCHSNER, M D

NEW ORLEANS, LA

FROM THE DEPARTMENT OF SURGERY, SCHOOL OF MEDICINE, TULANE UNIVERSITY, NEW ORLEANS, LA

THE PREVENTION of ischemic gangrene following occlusion of the major peripheral arteries has been studied since the time of Petit who, in 1731, observed the local effects of ligation of an artery. The results of occlusion of the major peripheral vessels have been extensively investigated, both clinically and experimentally. These studies have resulted in a fairly complete understanding of the underlying pathologic physiology. Following major peripheral arterial occlusion certain changes occur, many of which are commonly accepted, whereas some are considered speculative. One factor common to all major arterial occlusions is a decrease in blood supply distal to the occlusion, resulting in ischemic changes varying from necrosis of a few cells to massive gangrene of an entire extremity.

The prevention of ischemic gangrene following sudden occlusion of a major peripheral artery is desirable in all cases. The causes of this most undesirable complication and the methods of its prevention will be discussed in this presentation. The lesions of the peripheral vascular tree which are potential or actual causes of ischemic gangrene, in order of frequency are traumatic injuries, aneurysms, and arterial embolism. The usually employed surgical treatment in arterial injuries and aneurysms is sudden obliteration of the involved artery either by ligation or by suture, whereas in arterial embolism, arteriotomy and arteriorrhaphy have been the so-called procedures of choice.

The peripheral arterial system is composed of a main artery with secondary branches (collateral circulation), capillaries (both arterial and venous), venules, and main collecting venous trunks. The vessels as far as the capillaries are neuromuscular tubes through which the blood circulates to supply the component parts of an extremity with both nourishment and oxygen. The veins are the disposal system which returns the used blood back to the heart and lungs. A third circulation is the lymphatic system which is dependent upon an intact vascular system for its normal function. The blood vascular system, with the exception of the capillaries, is under the influence of the sympathetic nervous system, which controls the caliber of the vessels and also to a certain degree the blood volume flow. Three essentials for a

* Read before the American Surgical Association, St. Louis, Mo., May 1, 2, 3, 1940

normal arterial blood volume flow are elasticity of the vessel wall, vasomotor balance, and cardiac output. The venous circulation is dependent upon vasomotor control, capillary pulsations, and a normal peripheral venous pressure (Kountz¹). In Kountz's perfusion experiments it was almost impossible to force the blood through the capillary bed when the veins had been previously emptied. However, with a tourniquet around the limb, elevating the venous pressure 10 to 20 Mm Hg, a maximum arterial flow occurred. From this investigation he concluded that peripheral venous pressure has an important influence on the passage of blood through the capillaries. According to him, Silbert, Lilienthal, Collens and Wilensky observed the same phenomena clinically in peripheral vascular diseases. Therefore, it is necessary that a certain residual pressure be present both on the arterial and venous sides to maintain normal peripheral capillary circulation.

That the third circulation, or lymph flow, is dependent upon the normal blood flow (arterial and venous residual pressure plus capillary pulsation) has been demonstrated experimentally by Monterio,² and McMasters and Parsons.³ McMasters and Parsons, and Cressman and Blalock⁴ showed experimentally that capillary pulsations were necessary for the lymph flow. Monterio demonstrated that by increasing the peripheral residual pressure by sympathectomy there occurred an increased lymph flow in the extremities. Therefore, we are justified in assuming that a normal peripheral circulation (arterial, venous, and lymphatic) is dependent upon a residual arteriovenous pressure, capillary pulsations and sympathetic balance. Any alteration in arterial or venous pressures, blood volume flow, or sympathetic control will produce marked disturbances in normal function. When these become irreversible, permanent tissue damage results.

It is well known that ischemic gangrene does not always follow occlusion of a major peripheral artery. The necrosis is prevented in such an instance by the maintenance of an adequate blood supply through the collaterals. In both the upper and lower extremities there is an abundant collateral circulation which never functions to its full capacity as long as the main vessels function normally. It is only when the main artery is occluded that the collaterals take over the function of the occluded vessel. The functional capacity of the collateral circulation to compensate for major arterial loss varies according to site of obliteration, *i.e.*, there are certain anatomic locations in which the main arterial circulation is most vulnerable, due to a deficient collateral vessel anastomosis. The obliterations of the common femoral, carotid at its bifurcation, and the popliteal arteries are frequently followed by grave consequences. The collateral circulation around the shoulder, elbow, hip, hand, and foot is very abundant (Figs 1, 2 and 3). The collaterals around the knee are rather scant because there are no great masses of muscle bridging the knee joint (Sehrt⁵).

The function of the collaterals is to maintain adequate blood supply to the tissues of the body. In reality they are nothing more than arterial branches that originate from the main parent arterial stem. They, in turn,

break up into an extensive capillary network in the bone, muscle, subcutaneous tissue, and skin. They are under control of the same sympathetic system which controls the main artery. Therefore, any disturbances, direct or reflex within the main arterial stem affect the collaterals secondarily. Probably the

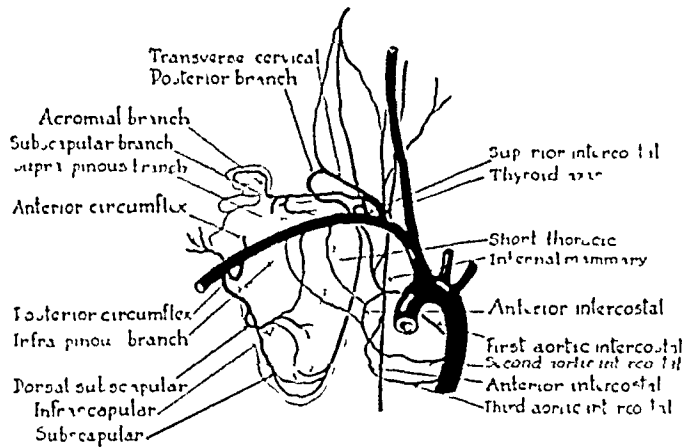


FIG. 1.—Illustrating the extensive collateral circulation extending from subclavian to the upper extremity. Figure 1 blends into Figure 2.

most important function of the collateral vessels is the substitution of an efficient circulation to an extremity in which the main stem artery has been obliterated. In fact according to Matas,⁶ the important results for the successful obliteration of the main artery of an extremity are dependent upon

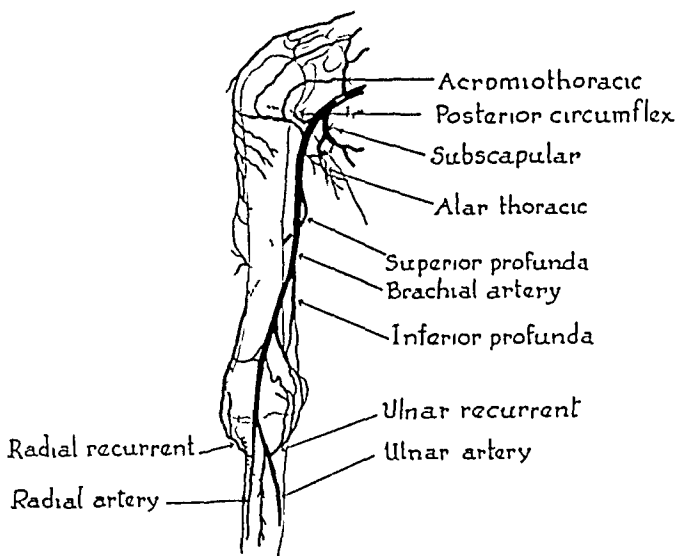


FIG. 2.—Drawing showing the collateral circulation bridging the axillary to brachial. The illustration also demonstrates the collateral vessels of the entire upper extremity.

the efficiency of the collateral circulation. It is, therefore, an indubitable fact that the incidence of ischemic gangrene following sudden occlusion of a major artery of an extremity is dependent upon the inadequacy of blood volume flow through the collateral vessels, and varies from 52 per cent⁷ to

45.8 per cent.⁸ The incidence varies greatly in the different types of obstruction. In traumatic lesions the incidence of ischemic gangrene varies from 11 per cent⁹ to 45.8 per cent,⁸ in ligations for aneurysms, 5.2 per cent⁷ to 15 per cent,¹⁰ and in embolic obstruction it is probably highest of all, averaging over 30 per cent.^{11, 12}

In traumatic lesions of the main arterial trunks of the extremities, the incidence of gangrene, according to Tuffier,¹³ is 40.2 per cent. Heidrich¹⁴ reported an incidence of 15.5 per cent of ischemic gangrene in 995 cases following ligation of the large peripheral arteries. Kietzschmann⁹ reported an incidence of 11 per cent gangrene requiring amputation in a series of 72 cases of traumatic lesions involving the peripheral arteries. Makins,⁸ in 101

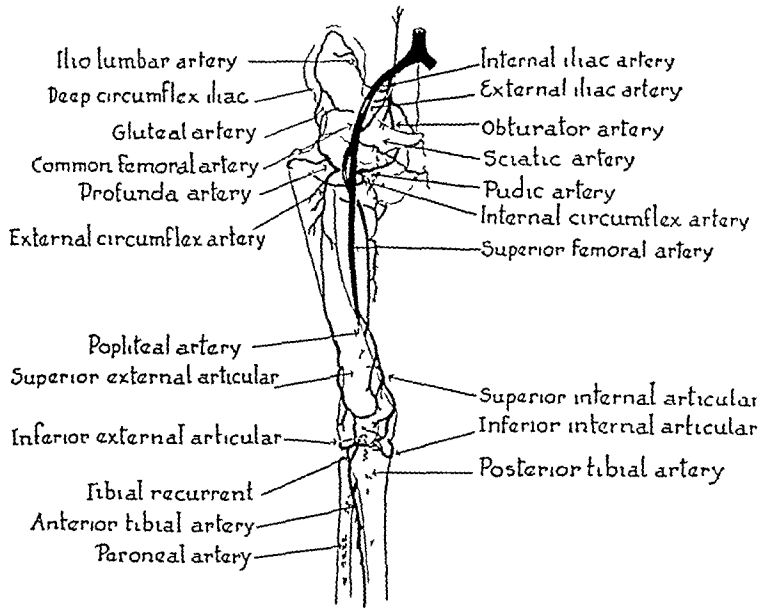


FIG. 3.—Drawing showing the abundant collateral circulation bridging the iliacs to the femoral. The collateral circulation bridging the popliteal is also illustrated.

cases of war wounds of the major peripheral arteries, had an incidence of 28 per cent ischemic gangrene. Sehart,⁵ in 1938, stated that ligation of the main artery in the lower extremity resulted in gangrene in 20 per cent, whereas ligation of the axillary artery resulted in ischemic gangrene in only 7.8 per cent. That the incidence of ischemic gangrene varies following occlusion at different levels of the same artery as well as the different major arteries of the extremities, is demonstrated by the following statistics: subclavian, 25 per cent, axillary, 16.6 per cent, brachial artery, 23 per cent, femoral, 25 per cent, popliteal, 41.66 per cent, tibial, zero per cent, carotid, 33.33 per cent (Makins⁸). Makins stated that there was considerable variation in the incidence of gangrene following injury to the popliteal artery according to the location of the arterial injury. In 15 cases with injuries in the upper third gangrene occurred in three (20 per cent), in 25 cases with injuries in the middle third, gangrene occurred in ten (40 per cent), and in 20 cases with injuries in the lower third, gangrene occurred in seven (35 per cent). These significant variations in the incidence of gangrene at

various levels of the popliteal are dependent upon the anastomosis about the knee. Tuffier¹¹ reported an incidence of 41.16 per cent gangrene following injury to the popliteal artery in 24 cases, and stated that, in general, ligation of the arteries at the roots of the limbs results in ischemic gangrene in 40.2 per cent.

In the majority of traumatic lesions of the peripheral arteries, the preferable treatment is the ligation of the injured vessel, which results in its sudden occlusion. The injury plus the sudden occlusion produces pathologicophysiology changes that are responsible for the high incidence of ischemic gangrene. The rapid progression of this process also prevents the development of an adequate circulation. Both the pathologicophysiology and collateral developments will be discussed later.

Sudden arterial occlusion by an embolus produces an incidence of ischemic gangrene comparable to the incidence occurring following traumatic arterial lesions. Both produce sudden occlusion and the pathologic physiology is very similar. Danzis¹¹ reported 129 cases of arterial embolectomy with an incidence of gangrene in 39.5 per cent. Linton¹² collected 282 cases of arterial embolectomy, in only 30 per cent of which was there a return in circulation. In a personal series of 44 emboli occurring in 36 patients, of whom only 12 were operated upon the incidence of ischemic gangrene necessitating amputation was 67 per cent. In another series of 17 cases, treated symptomatically, ischemic gangrene developed in 12 or 70 per cent. In arterial embolism, as in ligation for arterial trauma, there is a sudden occlusion of the main artery of an extremity without sufficient time for the collateral circulation to develop, with the result that the high incidence of ischemic gangrene is due to failure of the peripheral circulation.

In contrast to the above is the low incidence of ischemic gangrene following sudden occlusion of the major artery of an extremity for the cure of aneurysm. Matas⁷ reported an incidence of 5.2 per cent in 154 cases of aneurysm. Bid,¹⁰ on the other hand, estimates that the incidence of gangrene following occlusion of the popliteal artery for aneurysm varies from 8 to 15 per cent. The low incidence following treatment of aneurysms is due to the fact that (1) the aneurysm results in an interference with the normal blood volume flow, which is more marked in arteriovenous aneurysms than arterial, and (2) there is sufficient time for the estimation of the collateral efficiency and the development of the collateral circulation in cases in which it is found deficient. This contention is demonstrated by De Fourmestiaux's¹³ statistics as follows: in ligating the common carotid for hemorrhage, the mortality was 54 per cent, for tumors, 46 per cent, for arterial aneurysms, 13.5 per cent, and for arteriovenous aneurysms, 7 per cent—demonstrating also that the arteriovenous fistula develops a more abundant collateral than the arterial type.

The sudden occlusion of a major peripheral artery produces a typical syndrome which is familiar to the majority of surgeons. This is characterized by pain and sudden cessation of the peripheral pulse, followed by various

color changes in the skin, lowering of the surface temperature, numbness, and varying degrees of functional loss

According to Peaise,¹⁶ there is a definite elevation in arterial pressure proximal to the point of occlusion, the height of the pressure varying with the caliber of the vessel occluded. There was a marked fall in arterial pressure distal to the ligature in all of his experiments. He stated that this fall in systolic pressure never returned to normal. Wilson,¹⁷ in a large series of well controlled experiments, reported some interesting findings following the occlusion of the main artery to an extremity. Following ligation of the main artery of the hind leg of the rabbit, the carotid pressure rose from 138 to 144 Mm Hg, whereas the arterial pressure distal to the ligature fell from 128 to 78 Mm Hg, a drop of 50 Mm. The venous pressure dropped from a normal of 6 to 3.8 Mm Hg. A fall in peripheral venous pressure is a very serious handicap to the reestablishment of blood volume flow, as demonstrated by Kountz¹ in his perfusion experiments upon amputated lower extremities. He stated that when the veins were emptied before amputation it was almost impossible, by perfusion, to force modified blood through the capillaries. However, on elevating the venous pressure 10 to 20 Mm Hg by applying a constrictor, normal blood flow was established. The arterial volume flow per minute fell from 95.60 to 30.46 cc. There also occurred a cessation of arterial pulsations distal to the occlusion. It is seen from these experiments that both arterial and venous limb pressures fell markedly and that the mass of blood in the extremity and the volume flow of blood per minute were greatly diminished. He further demonstrated that the oxygen consumption per minute of the tissues of the whole limb and of the tissues below the obstruction was diminished. Mulvihill and Harvey¹⁸ demonstrated experimentally that ligation of a major peripheral artery resulted in the decrease of from 10° to 30° F temperature in the involved extremity. However, a return of the temperature of the extremity to its previous level occurred in about 13 hours after ligation of the main artery to the limb. They believed that this return of the temperature to normal was a vasomotor phenomenon, which they later proved by blocking the sympathetic vasoconstrictor fibers. Theis¹⁹ demonstrated that there is a definite fall in arterial pressure following ligation of the femoral artery in the dog. The blood pressure remained 10 to 30 Mm Hg lower distal to the arterial occlusion and it failed to return to normal at any time during a seven months' observation. The results of Hamovici's²⁰ experiments explain the phenomena resulting from the sudden occlusion of a major peripheral artery. This author introduced a balloon into the major peripheral artery of a dog's extremity. It was possible to distend the balloon to variable pressures. He was able to partly occlude the vessel, occlude the vessel slowly, or produce a sudden complete occlusion of the vessel. He observed that there was no vasomotor reaction if the vessel was incompletely obliterated and similarly no reaction occurred if the lumen was slowly obliterated. However, if sudden complete occlusion was produced, a marked vasomotor response occurred. This response

consisted of vasospasm in the region of the obstruction, vasospasm in the distal vessel, and arterioles and even the capillaries were affected. He also stated that this vasospasm could extend to the collaterals and manifest itself in the neighboring vessels even at a distance from the occlusion. Haimovici²⁰ called this vasomotor reaction "arterial colic," and refers to the pain accompanying vasoconstriction of the vessels as such. Haimovici's experimental observations are confirmed clinically by the manifestation in arterial occlusion by embolism and thrombosis. If the arterial embolus is not occlusive but secondary thrombosis slowly takes place, practically no vasomotor disturbances occur. This is because vasoconstrictor impulses affecting the collaterals are not initiated, and, also, because there is adequate time for the development of a collateral circulation. Conversely, if the lumen is suddenly occluded by an embolus, vasoconstrictor impulses originate at the site of the embolus and spread to all the arterial ramifications including the collaterals, and the process progresses so rapidly that there is insufficient time for the development of collaterals. It is evident that both experimental and clinical investigations are comparable and substantiate each other. Therefore, the major symptoms following occlusion of a peripheral artery are dependent primarily upon the cessation of blood volume flow through the artery distal to the ligature and secondarily upon the initiation of vasospasm which may spread to the entire vascular tree as described by Haimovici.²⁰

It is common knowledge that trauma to a large peripheral artery produces vasospasm at the site of the trauma which not infrequently spreads to the whole vascular tree. We have seen several cases of segmental arterial spasm with concomitant involvement of the distal vascular tree associated with perivascular trauma resulting from a so-called "*Metzger Verletzung*" (butcher's injury). This injury occurs during the skinning of beef, and is the result of slipping of the knife, resulting in a stab wound on the upper medial aspect of the thigh and trauma either of the femoral vessels or the perivascular tissues in the upper end of Hunter's canal. Even though the femoral vessels are not divided in many instances, reflex vasospasm is of such magnitude that the clinical manifestations are identical with those of complete arterial section. Montgomery and Ireland²¹ collected 42 cases of traumatic segmental arterial spasm and added two cases of their own. We have, also, observed two cases of segmental arterial spasm of the brachial artery following fracture of the humerus. Following the injury the arm distal to the segmental arterial spasm and the forearm, including the hand, were cadaveric. There was no pulsation in the radial, ulnar, or brachial arteries distal to the injury. True vasospasm was proven by the immediate relief following novocain analgesia of the stellate ganglion, which produced an immediate return of color to the arm and pulsation in the distal arteries.

Halsted,²² Leriche,²³ Matas,²⁴ and La Roque²⁵ demonstrated, clinically, that spastic contraction of an artery at a point distal to the site of trauma incidental to handling large blood vessels occurs not infrequently. According to them, this spasm was the result of vasomotor response to stimuli

Matas²⁴ reported a case of temporary obliteration of the pulse distal to an aneurysm in which, at operation, a patulous lumen of the artery was demonstrated. According to Leiche,²³ ligation of a major peripheral artery initiates a vasomotor spasm of the vessels of the extremity, and because of this he advised double ligation with severance of the vessel between the ligatures instead of ligating in continuity.

We believe that there are varying degrees of venospasm occurring concomitantly with arterial spasm. The reverse has been proven both experimentally and clinically, *i e*, that in sudden occlusion of the deep major vein there occurs an associated arterial spasm which at times simulates arterial embolism. Uggeri and Massone²⁶ reported three cases of thrombophlebitis of the extremities with ischemic arterial manifestations. They divided the arterial ischemic reactions into three groups. Group I. The ischemic symptoms appear with or after the phlebitic signs. Group II. The signs of circulatory deficiency appear suddenly and to such a degree that it is difficult to differentiate them from those produced by primary arterial embolus. Group III. There are the same clinical manifestations as in Group II, except that the onset and the ischemic manifestations are less intense. As the arteries reveal practically no pathologic changes, the ischemic manifestations are due to vasospasm initiated in the thrombophlebitic lesion. DeBakey, Buich, and Ochsner,²⁷ in a series of experiments upon dogs, isolated a segment of the femoral vein between two ligatures, aspirated the blood from the segment, and injected an equal quantity of 40 per cent aqueous solution of sodium salicylate. They found that the peripheral volume pulsations decreased (52.5 per cent) following ligation of the vein, reaching a maximum within five minutes. When sodium salicylate was injected into the isolated segment producing a chemical phlebitis, the peripheral volume pulsations decreased (51.6 per cent). This decrease in the peripheral arterial pulsations did not occur if a previous sympathetic ganglionectomy had been performed. Conclusions deduced from their experiments in determining the possibility of an ipsilateral arterial and arteriolar vasoconstriction in femoro-iliac thrombophlebitis are as follows: "It is evident that a chemical irritant placed either in the lumen of the main vein of the extremity or in the perivascular tissue of this vein produces a marked diminution in the volume (51.6 per cent) of peripheral pulsations. However, interruption of the nerve pathways by local infiltration with procaine hydrochloride at the site of the chemical irritation or by resection of the lumbar sympathetic ganglia and chain abolish this effect. This would suggest, therefore, that the decrease in volume pulsations following chemical phlebitis and periphlebitis is due to vasoconstrictor impulses initiated locally by the chemical irritant and coursing through the sympathetic ganglia in order to reach the terminal arterial vessels of the extremity." Ochsner and DeBakey^{28, 29} also demonstrated that in clinical cases of femoro-iliac thrombophlebitis (phlegmasia alba dolens) there is marked decrease in the ipsilateral peripheral arteriolar pulsations which is probably responsible for the white color and decrease in surface temperature

in these cases. The ischemic manifestations in these can be abolished effectively by novocain block of the regional sympathetic ganglia. They believe that the manifestations in thrombophlebitis are due less to the associated venospasm than to a reflex arteriospasm.

Another circulatory disturbance to which we attach great importance is the interference of blood flow through the vasa vasorum in arterial spasm. As the vasa vasorum are the channels through which the vessel wall receives its nourishment, and as they are in juxtaposition to the musculature, we believe that in arterial spasm there is marked interference with the blood supply to the arterial wall. According to Cummins,¹⁰ even the endothelial lining of the arteries receives some of the nourishment from the blood carried in the vasa vasorum. It is likely that interference with nutrition to the endothelium even for a short interval will cause sufficient pathologic cellular changes in the intima to produce arteriolar thrombosis.

From the above discussion, it can be concluded that a sudden occlusion of a major peripheral artery produces the following pathologico-physiologic changes: (1) sudden obliteration of the peripheral pulse, (2) marked decrease in blood volume flow, (3) rapid fall in the temperature of the limb tissues, (4) temporary or even permanent cessation of capillary pulsations, (5) marked and sustained decrease in the arterial and venous residual pressures, (6) moderate to severe vasospasm of the entire arterial tree distal to the arterial obliteration, (7) decrease or cessation of lymph flow, (8) concomitant venospasm, (9) mass of blood in the limb and blood volume flow per minute greatly diminished, (10) interference with vasa vasorum circulation by the arterial vasospasm, and (11) pathologic changes within the vessel wall resulting in thromboses. Unless the above pathologic physiology is prevented, or immediately corrected after the first clinical manifestations ischemic gangrene, either segmental or massive, will develop and this may result in the loss of an extremity or, not infrequently, life itself.

In surgery of the major peripheral arteries, all of the above changes must be constantly kept in mind and methods must be instituted preoperatively and postoperatively to prevent their occurrence. A failure to appreciate these fundamental principles will only result in disaster.

To prevent the development of ischemic gangrene following surgery of the main peripheral arteries (which in the majority of instances consists of obliteration of the vessel by ligature), it is necessary to: (1) test the efficiency of the collateral circulation, (2) develop the collateral circulation when found deficient, (3) prevent segmental and diffuse arterial vasospasm, (4) prevent venospasm, (5) increase the blood volume flow through the collaterals and the main vessel distal to the ligature, (6) maintain capillary pulsations, (7) maintain lymph flow and spread, (8) increase peripheral residual pressure, (9) maintain a normal or elevated tissue temperature, (10) increase blood volume flow through the vasa vasorum, and (11) prevent thrombosis of peripheral arterioles and capillaries.

In testing the collateral circulation the following methods have been ad-

vocated Matas compressor, Moszkowicz' test, oscillometric readings, plethysmographic readings, and thermocouple readings. We are partial to the Matas compressor test because it produces occlusion of the involved artery, shunting the blood flow through the collateral vessels. In other words its application is identical to a temporary ligature without damage to the artery. The test is easily performed and gives accurate information as regards the efficiency or inefficiency of the collateral circulation during obliteration of the main peripheral artery. Moszkowicz's test is mainly used to determine the site of amputation in the presence of peripheral gangrene and is not applicable to the subject under discussion. The other tests are important in determining the presence or absence of as well as the degree of vasospasm, but they do not give reliable information concerning the collateral efficiency, because the main vessel is patent. However, when used in conjunction with the Matas compressor they are invaluable because the degree of vasospasm can be accurately determined following the obliteration of the main peripheral artery by the compressor. The above test can be used only in elective surgery of the large peripheral arterial trunks. In the elective cases there is ample time for prolonged study, and all the information regarding collateral circulatory efficiency, vasospasm, venous pressure, residual arteriovenous pressure, tissue pressure, and tissue temperature can be obtained with safety, preoperatively. However, in traumatic lesions of the major peripheral arteries and in sudden occlusion by an embolus, the time element precludes accurate study and testing of the efficiency of the collateral circulation. In the vast majority of traumatic lesions the patient is in shock, therefore, many of the tests advocated above would be contraindicated. Even if they were used, the results would be of little significance because experimental results and clinical observations have demonstrated that in the traumatic lesions as well as in sudden and complete embolic occlusions, the collateral circulation is inadequate due to the pathologic physiology induced by vasospasm. Therefore, methods must be employed that will establish and maintain an efficient collateral circulation, increase the blood volume flow, and at the same time prevent arteriovenous vasospasm of the peripheral vascular tree. As the incidence of gangrene is in direct proportion to the efficiency of the collateral circulation, the methods employed to prevent ischemic necrosis are mainly those of developing an adequate and sustained blood volume flow through the primary and secondary collateral vessels.

The methods used to develop the collateral circulation are divided into the following groups: (1) spontaneous, (2) mechanical, and (3) physiologic. The spontaneous development of a collateral circulation is the result of incomplete and gradual interference with the blood flow through the main peripheral artery. This commonly occurs in peripheral aneurysms, of which the arteriovenous type is likely to develop a more efficient collateral circulation than the arterial. This is because an arteriovenous aneurysm in the majority of instances produces a greater interference to the arterial blood flow at the site of the fistula. The obstruction to the blood flow by an arterial

aneurysm depends to a great extent upon the type and saccular form of the aneurysm. However, a good preoperative collateral circulation in an aneurysm is no warranty that it will be maintained postoperatively. The statistics of Matas,⁷ Bird,¹⁰ and De Fourmestiaux¹⁵ demonstrate that spontaneous development of the collateral circulation is common in aneurysms.

The mechanical methods used to develop the collateral circulation in order of their efficacy are the Matas compressor, intermittent venous occlusion (including the Pavaex), and simultaneous ligation of the concomitant vein. The Matas compressor obliterates the main artery above the arterial lesion shunting all the peripheral circulation through the collaterals distal to the point of obliteration. The compressor is applied daily for increasing intervals of time until an adequate collateral circulation has been established. The time required to obtain the desired results is occasionally considerable and, therefore, can be used only in the elective cases of vascular lesions. It cannot be used as an emergency procedure. Therefore, it is of little value as a preparatory method in traumatic lesions and peripheral arterial embolism.

The intermittent venous occlusion and the passive vascular exercises have the same limitations of application as the Matas compressor as a preoperative method in all but the elective cases. Both of these mechanical methods are more frequently used in the presence of an inadequate collateral circulation in progressive organic disease of the peripheral arteries. However, they might be used postoperatively to advantage, if the collateral circulation manifests evidence of beginning failure.

Simultaneous ligation of the concomitant vein when a large peripheral artery is ligated has been used rather extensively over a period of years in an attempt to increase the blood volume flow through the peripheral capillaries. Von Oppel¹¹ was probably the first to advocate ligation of the concomitant vein when a large peripheral artery was ligated. However, Makins⁸ states that it was possible that John Hunter ligated the accompanying vein in his first three cases of ligation of the femoral artery for aneurysm. Since von Oppel's first report considerable clinical and experimental data have been presented in favor of and against the procedure. Von Oppel¹² ligated the popliteal satellite vein simultaneously with the popliteal artery in six cases of peripheral vascular disease. He noted a marked change in the color of the foot corresponding to an increased collateral circulation. He believed that the vein ligation inhibited to a certain degree the incidence of ischemic gangrene. Holman¹³ states "that the evidence, amid the welter of many inconclusive experiments, proves beyond doubt the beneficial effect produced upon the nutrition of a limb by the simultaneous ligation of artery and vein." Tuffier¹⁴ recorded an incidence of ischemic gangrene of 41.66 per cent following ligation of the popliteal artery and an incidence of 40.2 per cent following ligation of all large peripheral arteries at the root of the limbs. In cases in which there was simultaneous ligation of artery and vein (popliteal) the respective incidences were 21 per cent and 24.5 per cent, almost a 50 per cent reduction. Heidrich¹⁴ reported a series of 198 arterial ligations with simultaneous ligation

tion of the satellite vein with an incidence of only 8.5 per cent gangrene. Whereas, in 995 cases in which the artery alone was ligated, the incidence was 15.5 per cent. Makins⁶ reported a 28 per cent incidence of gangrene in 101 cases in which the artery alone was ligated and a 19.7 per cent incidence in 71 cases with simultaneous ligation of the artery and the vein. Brooks,³⁴ after extensive experimental work, concluded that this procedure is of immediate benefit in decreasing the incidence of gangrene, but cautions against the late effects in promoting venous stasis. He advocated ligation of the concomitant vein when the common femoral, common carotid, and popliteal arteries were ligated, because occlusion of these arteries is frequently followed by gangrene. According to Coudray,³⁵ ligation of the internal jugular vein simultaneously with the carotid diminishes the risk of hemiplegia. Sehit⁵ reported an incidence of 20 per cent gangrene following ligation of the main peripheral artery of the lower extremity. However, when the vein and artery were ligated concomitantly the incidence fell to 9 per cent. In a very excellent and well-controlled experimental investigation of the effects of simultaneous ligation of major peripheral arteries and veins, Wilson¹⁷ found that when the femoral artery was ligated the peripheral arterial pressure dropped from 138 to 78 Mm Hg, the venous pressure dropped from 6 to 3.8 Mm Hg, and the blood volume flow per minute fell from 95.60 to 30.46 cc. When artery and vein were simultaneously ligated the arterial pressure dropped from 138 to 94 Mm Hg, the venous pressure was elevated from 6 to 22 Mm Hg, and the blood volume flow per minute decreased from 95.60 to 25.81 cc. Wilson concluded from his experiments that the simultaneous ligation of the concomitant vein does not lessen the incidence of ischemic gangrene which follows the ligation of the main artery of a limb, nor does it decrease the severity of or the distribution of muscle necrosis.

From the above statistics, it can be concluded that the simultaneous ligations of major peripheral arteries and veins diminishes but does not prevent the occurrences of ischemic gangrene. Wilson's investigations demonstrated that such a procedure causes a marked reduction in blood volume flow, which is undesirable. We believe that the procedure is not indicated because better results can be obtained by abolition of sympathetic impulses. Also as shown by DeBakey, Burch, and Ochsner²⁷⁻³⁰ simple ligation of the femoral vein of the dog produces a reduction of volume pulsations (52.5 per cent) in the foot. Although various methods have been used to decrease the incidence of ischemic gangrene following occlusion of major peripheral arteries, none has been universally successful. Because of the occasional failure in maintaining adequate circulation in such cases by means of the usually employed methods and because of the invariably good results which we have obtained from the use of physiologic method, *i.e.*, interrupting the vasoconstrictor impulses, we have abandoned all other methods in favor of this one. It is a method that can be used preoperatively, at the time of operation and postoperatively, in all operations upon the peripheral vascular system. It should be designated the

physiologic method because those impulses (vasoconstrictor) which are responsible for the diminution of the blood are prevented

Jaboulay,¹⁷ in 1899, proposed periarterial sympathectomy to increase the circulation in the extremities. Leriche,¹⁸ in 1913, performed periarterial sympathectomy upon the femoral artery and observed that the maximum effect occurred within 36 hours postoperatively. The effect was an increase in the arterial pressure "which usually became an hypertension," and also an increase in surface temperature. These effects, however, gradually disappeared. Leriche in 1913, stated that "the clinical phenomena following periarterial sympathectomy are in accordance with the experimental facts determined by Claude Bernard in 1832." Herrick, Essex, and Baldes¹⁹ demonstrated experimentally that there was an increased blood volume flow through the femoral artery of the dog following lumbar sympathectomy. They found that the

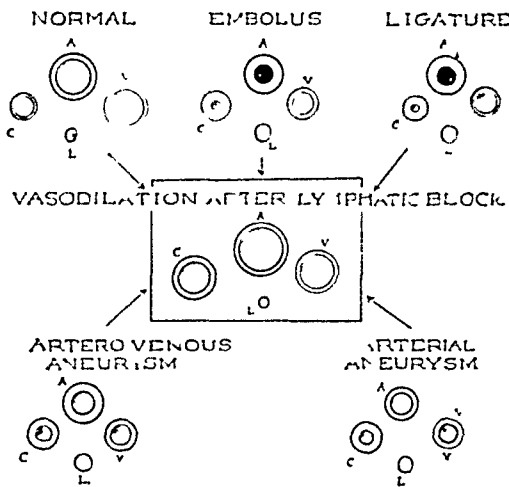


FIG. 4.—Drawing illustrating the effect of sympathectomy upon various occlusive conditions of the major peripheral vessels.

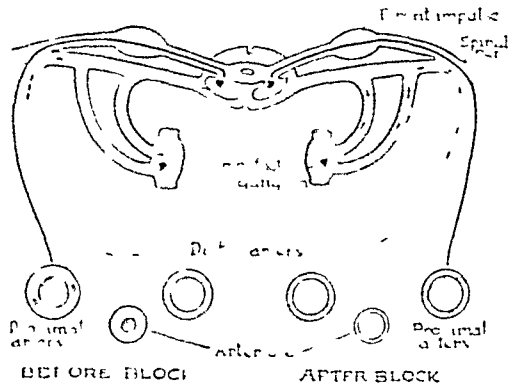


FIG. 5.—Demonstrating the effect upon the normal vessels and vasomotorum following sympathetic block.

increased flow was twice that of normal. They also observed at the same time that ether anesthesia produces an increase in blood flow equal to that produced by sympathectomy. The latter observation is of great significance because in ligating a peripheral artery the circulation may seem adequate at the time of the operation only to fail several hours later, the vasodilatation being due to the anesthesia.

Mulvihill and Harvey¹⁸ observed that there occurred constantly a fall in temperature of the extremity following ligation of the dog's iliac artery. However, such a decrease in temperature was obviated by the simultaneous performance of sympathectomy. On the basis of his experimental observations, Theiss¹⁹ found that following sympathectomy there was an increased blood volume flow through the collateral arterioles as well as an increase in both surface and deep temperatures. He also demonstrated that in the main artery below the ligature there was an increased blood volume flow of 60 volumes per cent, and a 15 per cent average rise in blood pressure. The author observed that the fall in the peripheral arteriole pressure upon the

sympathectomized side rapidly returned to normal and at the end of ten months was the same as the normal blood pressure. His conclusions were that sympathectomy preceding the ligation of the femoral artery in the dog resulted in an increased blood volume flow, sustained normal peripheral pressure, prevention of arterial vasospasm, and the immediate and rapid development of an adequate collateral circulation. This marked increase in collateral circulation remained constantly greater than the physiologic increase taking place in the unsympathectomized limb. This is demonstrated graphically in Figure 5 which demonstrates the effect of sympathectomy upon the normal peripheral vascular tree. Monteiro² has shown, experimentally, that there is a definite increase in the lymph flow of an extremity following lumbar sympathectomy. This is an important observation because in the absence of peripheral pulsations (produced by arterial occlusion and vasospasm), McMasters and Pai-

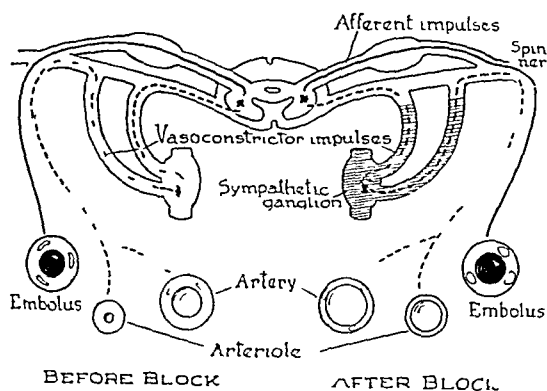


FIG 6—Illustrating the effect upon the peripheral vessels distal to sudden occlusion of the major artery by embolus or ligature right

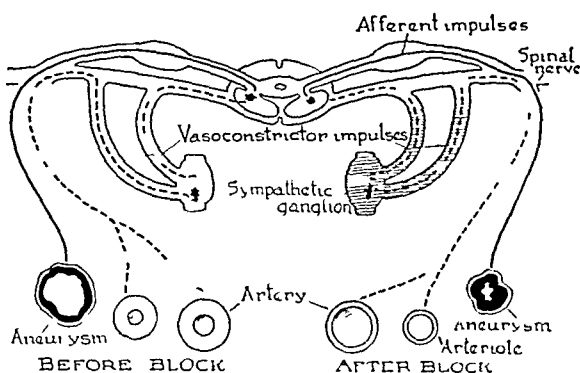


FIG 7—Illustrating the effect of sympathetic block upon aneurysms and the peripheral vessels

sons³ have shown experimentally that there is no flow of lymph. Cressman and Blalock⁴ have made similar observations.

As previously stated, in the presence of vasospasm the circulation through the vasa vasorum may be so decreased that a definite interference with nutrition of the vessel wall may result in intra-arteriole thrombosis. Griffith and his coworkers⁴⁰ have recently demonstrated, experimentally, that the vasa vasorum of the femoral artery in the rat are definitely increased in number, as well as in diameter, following sympathectomy.

From a critical review of the effects of sympathectomy upon the vascular tree in the normal and obstructed major peripheral arteries, it can be definitely stated that sympathectomy counteracts the pathologic physiology produced by occlusion of major peripheral vessels (Table I) (Figs 4, 6 and 7). Therefore, sympathectomy or sympathetic block (preferably the latter) as a therapeutic measure to prevent ischemic gangrene is definitely indicated in surgery of the major peripheral arteries. This method of developing the collateral circulation in surgery of the peripheral arteries was advocated by us⁴¹ in December, 1933. In 1939, we^{42, 43} again advocated this method as a preoperative therapeutic procedure to develop the collateral circulation and prevent the occurrence of ischemic gangrene in all surgical procedures upon the major peripheral arteries.

TABLE I

THE EFFECTS UPON THE PERIPHERAL VASCULAR TREE FOLLOWING OCCLUSION OF THE MAIN ARTERY	THE EFFECT OF SYMPATHECTOMY UPON THE PERIPHERAL VASCULAR TREE FOLLOWING OBSTRUCTION OF THE MAJOR PERIPHERAL ARTERY
(1) Spasm of main peripheral artery	(1) Vasodilation of main peripheral vessels
(2) Spasm of the collaterals	(2) Vasodilation of collaterals and increase in number
(3) Low arterial pressure distal to occlusion	(3) Return to normal of arterial pressure distal to occlusion
(4) Decreased peripheral venous pressure	(4) Return to normal of peripheral venous pressure
(5) Increased pressure proximal to occlusion	(5) Increased pressure proximal to occlusion
(6) Decreased blood volume flow per minute	(6) Sustained increased blood volume flow per minute through main artery and collaterals
(7) Decreased arteriolar pulsations	(7) Increased return of arteriolar pulsations
(8) Slowing and stasis of lymph flow	(8) Increased lymph flow
(9) Decreased flow through vasa vasorum	(9) Increased number and size of vasa vasorum
(10) Decrease in number of collaterals through which blood flows	(10) Increased number of collaterals
(11) Slow development of collaterals	(11) Rapid development of collaterals
(12) Degenerative changes in vessel wall	(12) Increased blood supply to vessel wall
(13) Occurrence of thrombosis	(13) Thrombosis extremely rare
(14) Muscle necrosis	(14) Increased blood supply to muscles
(15) Gangrene	(15) Ischemic gangrene prevented

Bird¹⁰ and Plotkin¹¹ have also recommended the procedure in all cases of popliteal aneurysm as a preoperative therapeutic measure to prevent postoperative ischemic gangrene.

Leiche¹³ has recently (1940) advocated sympathetic block in all cases of traumatic lesions of the major peripheral arteries in which ligation of the artery is necessary. In traumatic lesions of the peripheral arteries, we feel that in addition to the therapeutic methods advocated above, the intravenous injection of heparin (Murray and Best¹⁵) may be indicated to prevent secondary thrombosis resulting from trauma of the arterial wall. We do not advocate cervicodorsal or lumbar sympathectomy in such cases because we feel that the same results can be obtained by novocain and alcohol block of the sympathetic ganglia and chain.

Dos Santos¹⁶ stated that following arterial occlusion for the cure of arterial and arteriovenous aneurysms he performs repeated sympathetic block postoperatively until a satisfactory and sustained collateral circulation has developed. DeBakey¹⁷ stated that repeated novocain block of the sympathetics is preferable because a maximum response follows each block whereas if the sympathetic ganglia and chain are destroyed either by surgical removal or alcoholic destruction, the maximum response occurs for a short period and cannot be repeated. Moreover, another disadvantage of alcohol is the possibility of producing an alcoholic neuritis of the somatic nerves. Alcoholic

neuritis occurs in about 30 per cent of the cases following block of the cervico-dorsal sympathetics and in about 2 to 5 per cent of the lumbar injections

Technic—The technic of sympathetic block is not difficult and is practically without danger if only novocain or allied anesthetic drugs are used

For the cervicodorsal sympathetic block we prefer the anterior approach of Leiche modified by DeBakey. By this method, using 10 cc of 1 per cent novocain, the cervicodorsal ganglia are suffused with the anesthetic solution producing an extensive sympathetic block

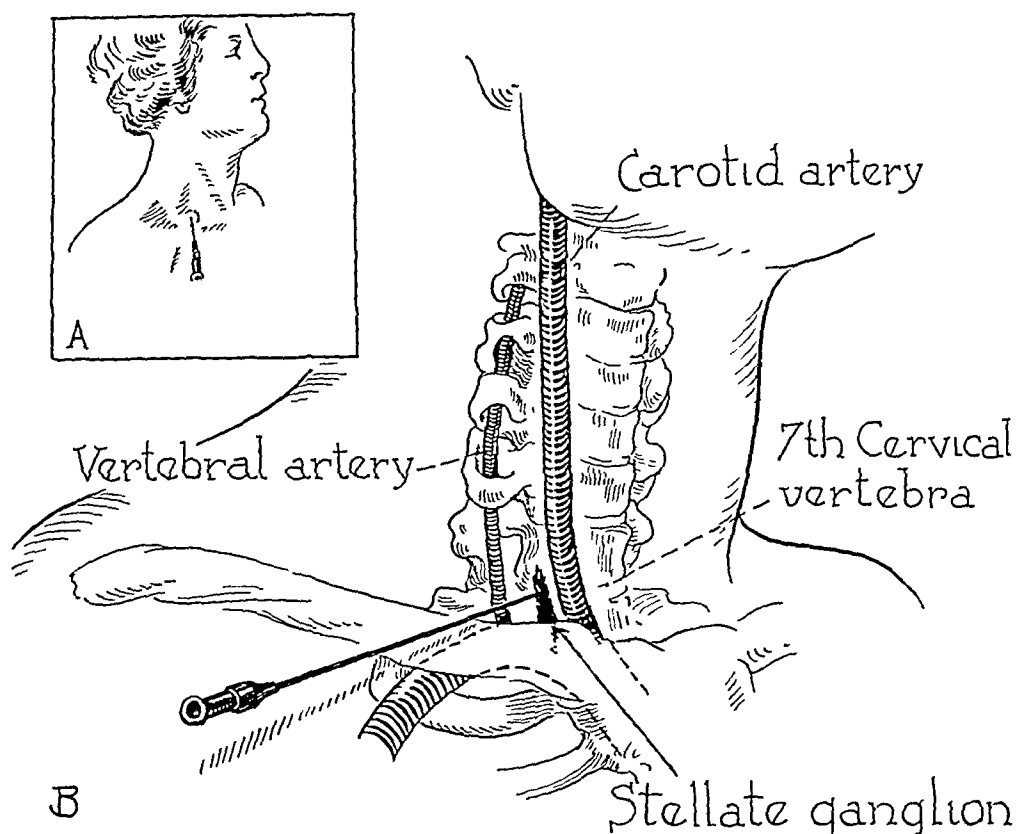


FIG 8—Drawing illustrating the technic for stellate ganglion injection. Insert shows anatomic landmarks used as a guide in the introduction of the needle

The patient is placed in a supine position with the head turned slightly to the opposite side. A point is selected 1 cm medial to the midpoint of the clavicle and immediately above its upper border (Fig 8). The needle (spinal puncture needle) is then introduced inward and backward at an angle of 45° with the midline until it impinges against the anterolateral surface of the seventh cervical vertebra. The needle may impinge against the seventh cervical or against the ligament between the seventh cervical and first dorsal. If no blood is aspirated, 10 cc of 1 or 2 per cent novocain is injected slowly. A successful block is indicated by the rapid appearance of a Horner's syndrome.

For lumbar sympathetic block, the patient can be placed either in the lateral position as shown in Figure 9 A or in the prone position with the lumbar vertebra and hips slightly elevated. The lumbar spinous processes are outlined by palpation. A point two fingers' breadth lateral to the upper border of the spinous process is located and a wheal of novocain injected intradermally to

mark the site of puncture. The first, second, third, and fourth lumbar transverse processes are so marked. A spinal puncture needle is now inserted vertically at each of the above cutaneous sites until the point impinges against the transverse process. The needle is then introduced for a distance of about 5 cm (two and one-half fingers' breadth) (Fig 9 C). Five cubic centimeters of novocain are now injected through each of four needles.

If it is decided to use alcohol, the needles are left *in situ* after injecting the novocain. The limb is observed for 20 to 30 minutes to determine whether

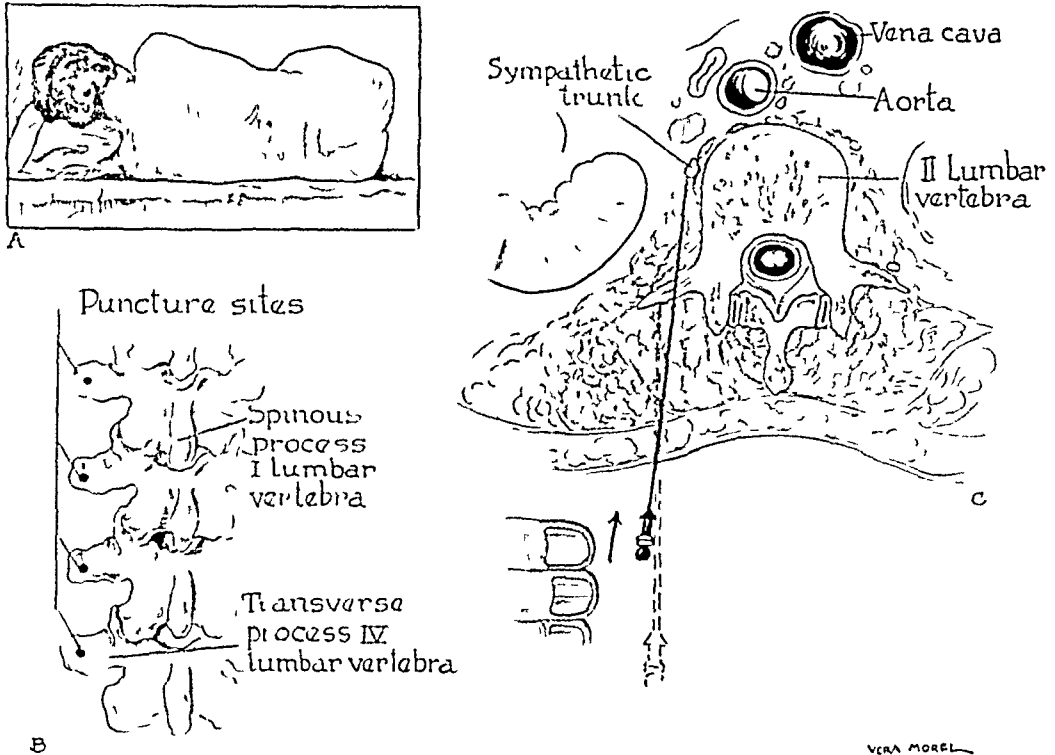


FIG 9.—Drawing illustrating the technique of injecting the lumbar sympathetic ganglionated chain. A Position of patient. B Points of contact of the needle with the lumbar transverse process. C The anatomic relations of surrounding structures to the needle.

the block has been successful. If successful the surface temperature will be elevated and sweating will be inhibited. Five cubic centimeters of 95 per cent alcohol is then injected through each of the four needles. Before removing the needles a few drops of novocain are injected through them to wash out the alcohol.

Results—We have employed the physiologic method, *ie* sympathetic block, of increasing the collateral circulation as a preliminary procedure to the ligation of major peripheral arteries in ten cases. In all but two of these cases the collateral circulation was found to be inadequate by the Matas compressor test. In the other two cases, one of which was an aneurysm of the common iliac and the other a stab wound of the common femoral, the test could not be applied. Of these ten cases, one was a mycotic aneurysm of the right common iliac artery. Following sympathetic block and ligation of the common iliac

at its origin, there was no change in color and no decrease in temperature of the corresponding extremity. There were two cases of arterial aneurysm of the femoral artery and three cases of popliteal aneurysm which were cured by obliterative endo-aneurysmorrhaphy. Three of the cases consisted of arterio-venous aneurysm, two of which were femoral and one was popliteal. These were treated by quadruple ligation. There was one case of stab wound of the common femoral which required ligation. In none of these cases of ligation of the major peripheral arteries treated by preliminary sympathetic block was there any evidence of ischemia or deficiency of the peripheral circulation.

We have also used sympathetic block in four cases of embolus of the femoral artery. In one case the embolus was removed after sympathetic block. The other three cases were not operated upon. In all these cases the classic clinical manifestations of arterial embolism were present. Following novocain block of the lumbar sympathetic ganglia and chain on the affected side, there was a loss of numbness and a return to normal of color and temperature of the extremity. In peripheral arterial embolism there is not only a high incidence of ischemic gangrene but a high mortality, the gangrene increasing the mortality. Therefore, we believe that sympathetic block will not only materially decrease the incidence of ischemic gangrene but will also lower the immediate mortality.

REFERENCES

- ¹ Kountz, William B. Reestablishment of Circulation in Extremities. *Arch. Phys. Therap.*, **20**, 157, 1939.
- ² Monterio, H. La lymphangeographie chez le vivant: methode, resultats et applications. *Bruyl. Med.*, **19**, 205, 1938.
- ³ McMasters, P. D., and Parsons, J. The Effect of the Pulse on the Spread of Substances through Tissues. *Jour. Exper. Med.*, **68**, 377, 1938.
- ⁴ Cressman, R. D., and Blalock, Alfred. The Effect of the Pulse upon Flow of Lymph. *Proc. Soc. Exper. Biol. and Med.*, **41**, 140, 1939.
- ⁵ Schrt, E. Über die Kunstliche Blutlehre von Gliedmassen und unterer Körperhälfte. Sowie ueber die Ursache der Gangran des Gliedes nach Unterbindung der arterie allein. *Med. Klin. Berlin*, **12**, 1338, 1916.
- ⁶ Matas, R. Testing the Efficiency of the Collateral Circulation as a Preliminary to the Occlusion of the Great Surgical Arteries, *ANNALS OF SURGERY*, **53**, 1, 1911.
Idem. Aneurysms. *Surgery of the Vascular System*. Keen's Surgery, **5**, 216, 1920.
Idem. An Operation for the Radical Cure of Aneurysms Based upon Arteriorrhaphy. *ANNALS OF SURGERY*, **37**, 161, 1903.
- ⁷ Matas, R. Endoaneurysmorrhaphy. *Surg., Gynec. and Obstet.*, **30**, 456, 1920.
- ⁸ Makins, G. H. Gunshot Injuries to the Blood Vessels. William Wood, 1919.
- ⁹ Kretzschmann, W. Results of the Treatment of Wounds of the Large Vessels—(1) Primary Ligation, (2) Primary Suture, (3) Primary Amputations, (4) Secondary Amputations, and (5) Conservative Treatment. 1936.
Idem. Leipzig Dissertation. *Surg., Gynec. and Obstet.*, **65**, 56, 1937.
- ¹⁰ Bird, Clarence. Sympathectomy as a Preliminary to Operation for Popliteal Aneurysm. *Surg., Gynec. and Obstet.*, **60**, 926, 1935.
- ¹¹ Danzis, Max. Arterial Embolectomy. *ANNALS OF SURGERY*, **98**, 249, 422, 1933.
- ¹² Linton, R. R. Acute Peripheral Arterial Occlusion and Its Treatment. *New Eng. Jour. Med.*, **216**, 871, 1937.

- ¹⁷ Juffier, M. I. A propos des plaies des artères. Bull et mem Soc de Chir de Paris, 43, 1469, 1917
- ¹⁸ Heidrich, L. Über Urtasche und Häufigkeit der nekrose bei Ligaturen Grösser Gefässstämme. Beitr z Klin Chir 124, 607 1921
- ¹⁹ De Fommestiaux, I. Les accidents cérébraux et oculaires consécutifs à la ligature de la carotide primitive. Paris Thesis No 202 1906-1907
- ²⁰ Pearce, H. I. The Immediate Effects of Arterial Ligation, Experimental Study. Am Jour Med Sci 175, 40 1928
- ²¹ Wilson, W. C. Occlusion of the Main Artery and Main Vein of a Limb. Brit Jour Surg 23, 303 1933
- ²² Mulvihill, D. A., and Hurvey, S. V. Thermic Changes after Arterial Ligation and Ganglionectomy. Jour Clin Invest 10, 423 1931
- ²³ Heiss, F. V. Effect of Sympathetic Neurectomy on the Collateral Arteriole Circulation of the Extremities, Experimental Study. Surg Gynec and Obstet 57, 737, 1933
- ²⁴ Humoviet, H. From a Review of the 46th French Congress of Surgery, October 4, 1937, Paris, Trans DeBakey, Michael, Surgery 3, 306 1938
- ²⁵ Montgomery, A. H., and Ireland, J. Traumatic Segmentary Arterial Spasms. JAMA 105, 1741 1935
- ²⁶ Halsted, W. S. The Effect of Ligation of Common Iliac Artery on the Circulation and Function of the Lower Extremity. Johns Hopkins Hosp Bull, 23, 191, 1912
- ²⁷ Leriche, René. Les maladies des ligatures moyens de les prévenir et de les traiter. Presse med, 1, 41, 1940
- ²⁸ Mitus, R. Some Experiences and Observations in the Treatment of Arteriovenous Aneurysms by the Intrascapular Method of Suture (Endoaneurysmorrhaphy) with Special Reference to the Transvenous Route. ANNALS OF SURGERY 71, 403, 1920
- ²⁹ La Roque, G. B. Ligation of the External Iliac Artery and Vein Above and Below a Communicating Bullet Wound of These Two Vessels. ANNALS OF SURGERY, 73, 261, 1921
- ³⁰ Uggeri, C., and Massone, A. La sintomatologia arteriole delle plebiti degli arti. Arch Ital di chir, 49, 429, 1938
- ³¹ DeBakey, Michael, Burch, G. E. and Ochsner, Alton. Effects of Chemical Irritation of a Venous Segment on Peripheral Pulse Volume. Proc Soc Exper Biol and Med, 41, 581, 1939
- ³² Ochsner, Alton, and DeBakey, Michael. Thrombophlebitis and Phlebothrombosis. South Surg, 8, 269, 1939
- ³³ Idem. Therapy of Phlebothrombosis and Thrombophlebitis. Arch Surg, 40, 208, 1940
- ³⁴ Cummins, Harold. Personal communication
- ³⁵ Von Oppel, W. A. Zur Operativen Behandlung der Arteriovenösen Aneurysm. Arch f Klin Chir, 86, 31, 1908
- ³⁶ Idem. Reduzierter Blutkrieslauf. Trans Internat Cong Med London, 1913, Sec Surg, p 189
- ³⁷ Holman, Emil. Arteriovenous Aneurysms. New York, Macmillan Co., 1937
- ³⁸ Brooks, Barney. Surgical Application of Therapeutic Venous Obstruction. Arch Surg, 19, 1, 1929
- ³⁹ Coudray, G. Considerations sur les plaies de la carotide primitive et leur traitement par la ligature. Presse med, 28, 886, 1920
- ⁴⁰ Burch, G. E., DeBakey, Michael, and Sodeman, W. A. Effect of Venous Pressure on Volume Pulsation. Proc Soc Exper Biol and Med, 42, 858, 1939
- ⁴¹ Jaboulay. Quoted by Leriche and Hertz ⁴⁵
- ⁴² Leriche, René, and Hertz, I. De l'action de la sympathectomie periarterielle sur la circulation peripherique. Arch mal du cœur 10, 79, 1917
- ⁴³ Herrick, J. F., Essex, Hiram, and Baldes, E. J. The Effect of Lumbar Sympathectomy

- on the Flow of Blood in the Femoral Artery of the Dog *Am Jour Physiol*, 101, 213, 1932
- ⁴⁰ Griffith, J Q, Zinn, C J, and Comroe, B I Effect of Sympathectomy on the Vasa Vasorum of the Rat *Arch Path*, 26, 984, 1938
- ⁴¹ Gage, Mims Mycotic Aneurysm of the Common Iliac Artery, Sympathetic Ganglion Block as an Aid in the Development of the Collateral Circulation in Arterial Aneurysm of the Peripheral Arteries *Am Jour Surg*, 24, 667, 1934, *Trans South Surg Assn*, 46, 473, 1934
- ⁴² *Idem* The Development of the Collateral Circulation in Peripheral Arterial Aneurysms In press
- ⁴³ *Idem* Arterial Aneurysms of the Peripheral Arteries, Method of Developing the Collateral Circulation In press
- ⁴⁴ Plotkin, T De Utilite de la sympathectomie a distance dans certaines operations pour aneurisme arterioso-veineux *Lyon chir*, 36, 563 1939
- ⁴⁵ Murray, D W G, and Best, C H Heparin and Thrombosis *J A M A*, 110, 118, 1938
- ⁴⁶ Dos Santos Personal communication
- ⁴⁷ DeBakey, Michael Personal communication

DISCUSSION—RUDOLPH MATAS (New Orleans, La) The excellence of Doctor Gage's presentation suggests a contrast between the past and present methods of introducing papers at these meetings which are no doubt best appreciated by the older members, who, like the speaker, have lived to enjoy the modern outlook, so strikingly exhibited by Doctor Gage With the marvelous aid of contemporary cinematography and short, crisp, tabloid, lantern-slide condensations, a long dissertation is abridged with enormous economy of words without sacrifice of lucidity or precision Formerly, we spoke of a bird's-eye view of a scene or subject Now, we survey an encyclopedic panorama with all the speed, sweep and effectiveness of an airplane view In this way, our surgical programs are being made increasingly attractive and instructive by their pictorial and epitomized visualizations

The salient feature of Doctors Gage and Ochsner's thesis is their advocacy of alcoholic injections ("chemical section") of the regional neuroganglionic sympathetic, as a preventive of ischemic gangrene in all operations that may necessitate the occlusion, excision or obliteration of the major peripheral arteries Their experience, well-backed by others has given them confidence in the value of the vasodilator effect of neuroganglionic alcoholization as an effective means of accelerating and dilating the collaterals when the circulation in the main artery is suddenly blocked by a ligature for arterial wounds, for aneurysm, or, when angiospasm, an embolus or a thrombus blocks the circulation

Based upon their experience, the authors advocate the pre- and postoperative practice of chemical ganglionectomy by alcoholic injections as a systematic, or routine procedure, in all occlusive operations upon the main arteries of the upper and lower extremities

When ischemic gangrene follows the ligation, or other obstacle to the circulation, in the main artery of a region or extremity, the fatal ischemia is attributed to a failure of the collaterals to carry on the circulation beyond the ligation or obstacle The causes of this failure of the collaterals are numerous including the classic pathogeny, namely, congenital anatomic defects, chronic and acute arterial disease, relative viability of the tissues or organs involved in the ischemic area, stasis from venous obstruction, profound anemia and the

cardiocirculatory failure of hemorrhage and shock, with vasoconstriction or angiospasm as a contributing factor, *etc*

Since the benefit of sympathetic neuroganglionic alcoholization is dependent upon vasomotor paresis, with secondary dilatation of the arteries in the vascular bed, an activation of the collateral circulation is expected to follow the vasoparetic overflow. While the vasodilating effect of the alcoholic injections would indicate this procedure as especially effective in the rare cases in which angiospasm is a dominant factor, it is logical to believe that the vasodilating effect of the injection would also benefit the local anemias that are still responsive to sympathetic influences. Unfortunately, the patients who would be most benefited by vasodilation are, in the majority, victims of chronic or acute vascular disease—the senile and presenile arteriosclerotics, the thromboangitic, and others who are largely unresponsive to vasomotor control.

The importance of the relative viability of the tissues or organs supplied by the ligated or obstructed artery in determining the necrogenic effect of an acute ischemia is well exemplified in the coma and brain disorders that follow carotid ligations, and in the necrotizing effect of embolic obstructions in the pulmonary, the mesenteric and other splanchnic infarctions. Again, quite apart from arterial disease as a cause of ischemic gangrene are the ligations of the great vessels in young soldiers who are picked up from the battle field exsanguinated, shocked, after days of long exposure to cold and nights of sleepless vigilance and terrifying experiences. Under such conditions the ligation of the main artery of a limb is almost sure to end in gangrene, and in coma and death, if the carotid is ligated. In such cases, any attempt to prevent an ischemic gangrene by sympathetic ganglionectomy would prove not only an illusion, but a therapeutic parody. The experience of military surgeons in modern warfare—especially since blood transfusion has come into vogue, as in the late civil war in Spain, in which “blood banks” and “canned blood” were more available than in previous wars—has demonstrated that the surest preventive of ischemic gangrene following the ligation of the great arteries, including the carotids, is blood transfusion, copiously and repeatedly administered, until a living and actively functioning cardiocirculatory balance is restored.

In considering the adoption of sympathetic ganglionic alcoholization as a routine procedure, we should remember the variations in the distribution of the collateral branches of the main arteries which in the upper extremity (subclavio-axillary tract) are so free and abundant that ischemic gangrene after the ligation of the subclavian and the arteries of the arm may be regarded as a negligible risk outside of the shocked and exsanguinated wounded previously referred to. I know, personally, of 49 ligations and band occlusions of the subclavian artery for aneurysm with only one partial gangrene of the hand.

It is only as a sequela to infected emboli or propagated thrombi that gangrene is to be feared in the subclavian tract.

We realize the seemingly improvident paucity of collaterals in the lower extremities as compared with the abundance in the upper extremity when extirpating tumors or obliterating aneurysms of the terminal popliteal which involve its tibioperoneal trifurcation. It is in dealing with the arterial wounds, lesions (aneurysms) and other obstructive circulatory disorders of the lower extremities that lumbar sympathectomy by alcoholization finds its most favorable field of application, though, even here as the patients advance in years, its value in the prophylaxis of surgical ischemia must be regarded only in the light of an adjunct or auxiliary function.

Despite the limitations of chemical ganglionectomy by alcoholization as a preventive of ischemic gangrene, it is a valuable addition to the resource of

vascular surgery in dealing with the special indications of the method. The experience of the authors, especially Doctor Gage, in aneurysm, fully attests its value in promoting the collateral circulation when there is reason to doubt its efficiency before operation. Despite my great interest in the prophylaxis of ischemic gangrene in the surgery of aneurysm, I have been able to do without sympathetic ganglionectomy by alcohol or otherwise, in my practice, but I have no doubt that the alcoholization of the lumbar ganglia would have hastened the development of the collaterals in some cases. Though fairly safe in the expert hands of the authors, the alcoholization of the lumbar ganglia by the paravertebral route cannot be regarded as an innocuous procedure. My long experience in paravertebral splanchnic anesthesia with novocain solution, when the Kappis method was in vogue, has made it plain to me how obstinate neuritic pains and paresthesiae in the distribution of the spinal nerves may result from the diffusion of the alcohol in the paravertebral spaces.

Again, in considering alcoholic sympathectomy as a routine procedure for the prophylaxis of ischemic gangrene, we may say that since the methods of testing the efficiency of the collateral circulation in the neck and extremities have become fairly dependable and generally available, we are able to determine beforehand, with close approximation, what the behavior of the limb will be after ligation of its main artery. If there is clear evidence that the collateral circulation is efficient, it would seem unnecessary to resort to a prophylactic lumbar sympathectomy by alcoholization, nor need we worry in dealing with an aneurysm in our choice between a radical and a conservative operation.

If there is proof that the temporary occlusion of the main artery with our mechanical compressor* applied precisely at the prospective site of the ligation is followed by prolonged pallor, indicative of an inefficient collateral circulation, we have time, at least in the majority of cases of aneurysm, to train and develop the collaterals by the method of direct intermittent mechanical compression which I introduced 38 years ago and have continued to use effectively ever since. This procedure, which Doctor Gage has utilized and described with great fidelity, is usually combined with other classic methods of developing the peripheral circulation, such as contrast baths, diathermy, intermittent negative and positive pressure exercises (Pavaex, Collens-Wilensky, de Takats, *et al*). When there is no hurry, the slow and simple methods of collateral training will do, but in acute, accidental injuries when ligations are required for the control of hemorrhage, and there is little opportunity for vascular exercises, the method of chemical lumbar ganglionectomy with alcohol will probably find, here, one of its most useful applications, as an adjunct to transfusion and other cardiovascular restoratives.

DR IDYS MIMS GAGE (New Orleans, La.) I not only wish to thank Doctor Matas for his kind discussion of our paper, but also to express my gratitude and deep appreciation to him for his many kindnesses, because his tutelage and constant encouragement have been of inestimable value to me.

We did not offer this procedure of sympathetic block as a "cure-all" but recommend it as another method for the developing and maintaining of adequate collateral circulation in the presence of sudden occlusion of a main peripheral artery. The procedure has given such excellent results in our hands that we wish to suggest its use to those interested in vascular surgery.

* Matas, Rudolph. *ANNALS OF SURGERY*, 53, 1-43, January, 1911. *Idem*. *Amer Jour Surg*, N S 24, 692-698, June, 1934.

CIRCULATORY DISTURBANCES PRODUCED BY EXTENSIVE ANGIOMATA OF THE LOWER EXTREMITIES ASSOCIATED WITH VARICOSE VEINS^{*}

WALTER ESTELL LEE, M D ,

AND

NORMAN E FREEMAN, M D

PHILADELPHIA, PA

FROM THE DEPARTMENT OF SURGERY, GRADUATE SCHOOL OF MEDICINE AND THE HARRISON DEPARTMENT OF SURGICAL RESEARCH UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA, PA

THE SIMPLE ANGIOMA is of significance chiefly because of its disfiguring appearance unless it happens to be situated in some vital organ. When it is freely connected with the general circulation, however, so that the pressure within the smaller vessels is raised, it may increase greatly in size. Under such circumstances, a lesion which was originally simply a "birth mark," unsightly but harmless, may alter its characteristics so as to give rise to serious symptoms. Not only may the circulation locally be impaired and lead to ulceration and gangrene, but the effects on the systemic circulation may be harmful.

Free connections between the angioma and the arterial side of the circulation lead to the formation of a cirroid aneurysm. The physiologic disturbances which result from this condition have been fully described by Reid¹ and Holman.² When the angioma is in the lower extremity and is freely connected with the venous side through veins with defective valves, it is subjected to increased pressure. Dilatation of the smaller vessels takes place and gives rise to symptoms, both local and general, which, though less spectacular than those accompanying the cirroid aneurysm, may be serious and incapacitating.

The symptom complex of extensive angiomata of the lower extremity with varicose veins was first described by Devouges,³ in 1856. This condition was found to be associated with osteohypertrophy and attention was directed chiefly to this aspect of the patient's picture. In 1869, Trelat and Monod⁴ reviewed the literature on osteohypertrophy and described the associated vascular lesions. Klippel and Trenaunay⁵ originated the term "*naevus variqueux osteo-hypertrophique*," in 1900. They gathered reports of 14 patients from the literature and described an additional case. Three variations of the symptom complex were encountered. Those with the angioma alone, those in which the osteohypertrophy was the outstanding feature, and, finally, those with associated varicose veins. In their experience, osteohypertrophy was frequently encountered. It was unusual not to find varicose veins. The varices were rarely seen in infancy but the patients developed varicosities at an early age. Varicose ulcers often developed. The peripheral pulses were normal but the skin temperature was higher on the affected side. Numerous reports of cases have since appeared in the French literature—Van Neck,⁶ in 1925, Pautrier and Ullmo,⁷ in 1928, Sorrel,⁸ in 1932, Gougerot and Lortat-Jacob,⁹

* Read before the American Surgical Association, St. Louis, Mo., May 1, 2, 3, 1940.

in 1934, Alajouanine and Thurel,¹⁰ in 1935, Radulesco,¹¹ in 1935, Pautier and Lang,¹² in 1937, and Touraine, Duperrat and Baudouin,¹³ in 1938. In this country, cases have been reported by Homans,¹⁴ in 1922, Reid,¹ in 1925, Kleinberg,¹⁵ in 1930, DeTakats,¹⁶ in 1932, and Wise and Lisansky,¹⁷ in 1938.

During the past year, we have observed three patients with extensive angiomata of the lower extremities which were in direct communication with the general circulation through veins with defective valves. The circulatory disturbances which these patients presented form the subject of the present communication.

CASE REPORTS*

Case 1—Hospital of University of Pennsylvania, No 40306 B L, white, female, age 17, was admitted to the Surgical Service of Dr I S Ravdin, with the complaint of a "sore and swollen" right foot and attacks of syncope on standing. The patient had a large angioma of the right leg extending from the crest of the ilium to the sole of the foot, which had given rise to no subjective symptoms, a large vein on the medial aspect of the thigh had, however, been injected at the age of 11. At the age of 12, shortening of this leg was noticed. Four months before admission she developed phlebitis of the right leg. After recovery from the acute attack, it was first noticed that the angioma became turgid and suffused when the patient was in the erect posture, and that she frequently fainted when standing.

Physical Examination—The patient was found to have varicose veins of the right leg which filled from the saphenous and from a communicating vein of the lower thigh. The angioma filled rapidly through these veins but the reflux could be prevented by the application of a venous tourniquet. On standing, as shown in the first section of Chart 1, the blood pressure fell from 135/85 to 90/70, and the pulse rate increased from 60 to 152. Upon release of the tourniquet, which had completely occluded the circulation above the knee, the volume of the right leg, measured by displacement of water, increased by 200 cc within the first minute, as shown in the top curve of Chart 2. On the left (normal) side, the increase was only 25 cc, as shown in the bottom curve of Chart 2. Specimens of blood were obtained simultaneously from the veins of both lower legs and from both femoral veins, and the color of the blood obtained from all the veins was the same. At operation, the right long saphenous vein was ligated at its junction with the femoral together with four large branches, each the size of a normal femoral vein.

After operation, the rate of increase in leg volume after release of the tourniquet was found to be reduced, as shown in the second curve of Chart 2. The blood pressure and pulse changes on standing were not as marked although, as the second section of Chart 1 illustrates, she still fainted in the erect posture. The angioma of the thigh and hip did not become suffused on standing but the veins of the lower leg still filled from above. She was followed for a year, during which time the tissues of the lower leg were supported with an elastic stocking. She was examined a year later and at this time she no longer fainted on standing. The third section of Chart 1 illustrates the changes in blood pressure and pulse when she stood up. Since the angioma of the lower leg still filled from above, the saphenous vein was ligated at the point where the communicating vein from the femoral emptied into it. Three months later, the increase in the volume of the lower leg after release of a tourniquet was only 90 cc, as shown in the third curve of Chart 2, and the blood pressure and pulse changes on standing were almost normal. As the fourth section of Chart 1 shows, there was no fall in systolic pressure, and only

*Within the past three months, all three of the patients described in this article have been operated upon for further ligation of communicating veins. In each case when the dissection has been carried out through the superficial angioma, difficulty in wound healing was encountered, apparently due to persistent oozing of blood from minute vessels. Healing was delayed and the period of hospitalization increased.

LEE AND FREEMAN

BL - Volume of Right Leg Below Knee After
Release of Arterial Tourniquet

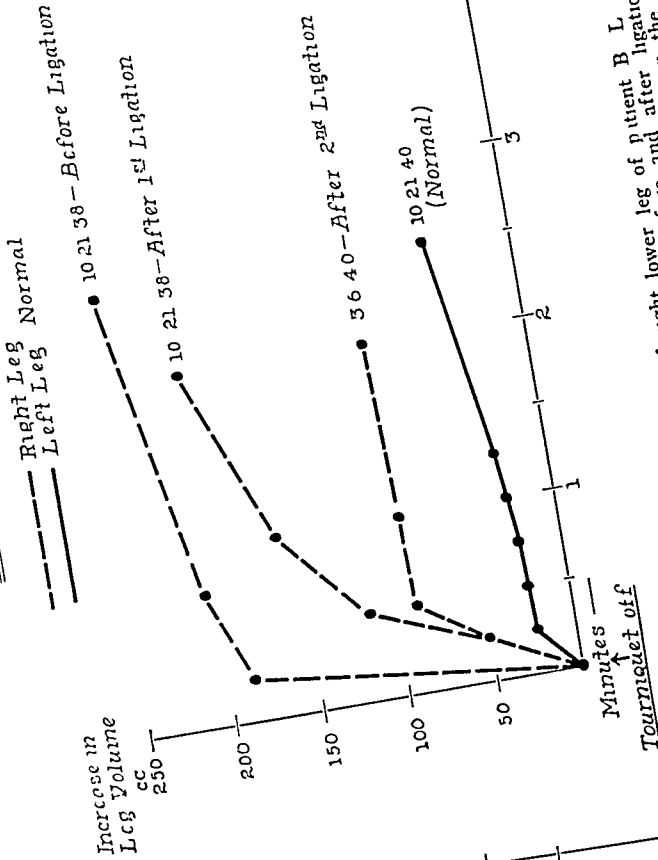


CHART 2—Increase in volume of right lower leg of patient B L after release of tourniquet applied above the knee, before and after ligation of the saphenous vein, and after ligation of communicating vein in the lower thigh. The increase in volume of the left normal leg under similar circumstances is shown in the bottom curve

BL - Cavernous Hemangioma with Varicose Veins

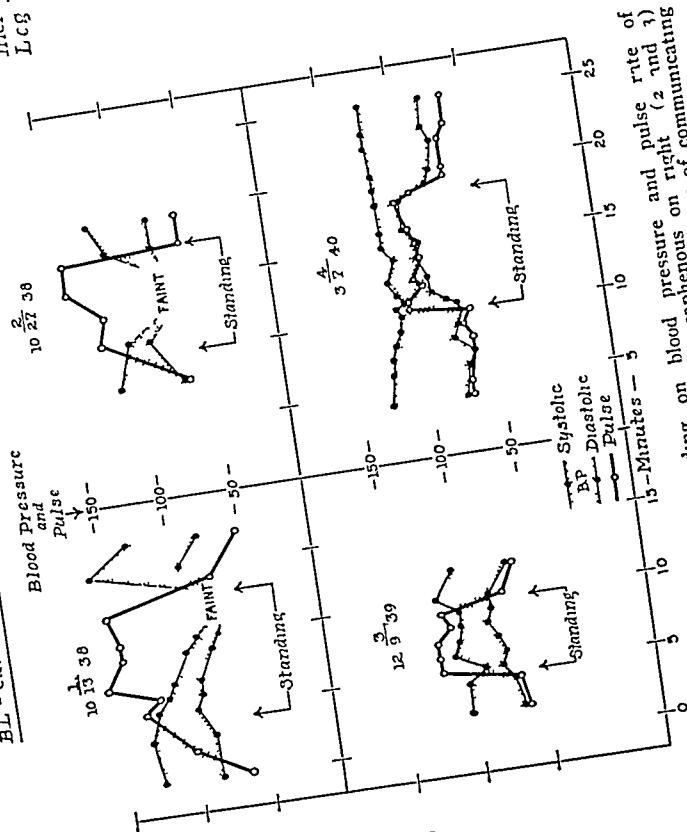


CHART 1—Effect of standing on blood pressure and pulse rate of patient B L (1) Before ligation of long saphenous on right (2 and 3) after ligation of long saphenous on right, (4) after ligation of communicating vein of lower thigh

a moderate rise in pulse rate. She was free from symptoms, and the angioma had decreased in size so that it was no more noticeable than it had been before her attack of phlebitis.

Case 2—Pennsylvania Hospital, No 36544. A. E., white, male, age 23, complained chiefly of pain and repeated attacks of phlebitis in varicosities of the right leg. At birth, he was found to have multiple angiomata of the right lower extremity, penis and right half of the scrotum. There was a general osteohypertrophy of both feet but particularly of the middle three toes of the right foot and the second and third toes of the left foot. The appearance of the feet is shown in Figure 1. Varicose veins of the right leg, first noticed at the age of 12, had been subject to recurrent attacks of thrombophlebitis with such severe pain that he developed a 60° flexion contracture of the right knee. During the period 1934–1937, he was operated upon four times for excision of thrombosed and varicose veins and correction of the deformity of the knee. On examination, it was found that the varicose veins of the right leg were in free communication with large blood sinuses on the posterolateral aspect of the thigh and leg. Figure 2 shows the location of these “lakes.” Their filling could be prevented by the application of a venous tourniquet to the upper thigh. The long saphenous vein was not involved, and the point of incompetence appeared to be in the region of the gluteal veins. With the patient lying “head down,” 30 per cent diodrast was injected into the top of this venous column and a roentgenogram taken. Figure 3 illustrates how the dilated vein was seen to pass through the fascia at the lower border of the gluteus maximus muscle and run up through the sciatic notch. An additional portal of entry appeared to be in the region of the superior gluteal vein. The varices of the upper portion of the buttocks also filled.

At operation, two large veins were divided at the inferior margin of the gluteus maximus. The tissue was extremely vascular and the bleeding was controlled with difficulty. After operation, the varices still filled from above but the filling was slower. Before operation, the pulse rate increased from 60 to 124 when he stood up. After operation, the pulse rate increased only to 104. Although the systolic blood pressure did not fall, there was an increase in the diastolic blood pressure in the erect posture. Further localization of the point of incompetent valves of the communicating veins is to be sought.

Case 3—Graduate Hospital of the University of Pennsylvania, No 142803. D. O., white, male, age 19, complained chiefly of edema of the legs and ankles. At birth, it was noticed that he had multiple vascular and other congenital anomalies. There was hypertrophy of the bones of both feet and the left upper extremity. Large angiomata were present over both lower extremities, penis and scrotum. The angioma on the left side extended from the level of the umbilicus and the crest of the ilium to the sole of the feet. The index and ring fingers of the left hand were fused. At the age of 12, he developed varicose veins of both legs. The left breast hypertrophied, and there was excessive growth of hair on this breast.

Physical Examination—The varices of the left leg were found to fill, largely, from the long saphenous system. On the right side, there was free communication between the angioma and the short saphenous system but filling on both sides could be prevented by the application of venous tourniquets. The appearance of the feet and legs is shown in Figure 4. The angiomata became suffused with blood when the patient stood up, while the blood pressure fell from 120/70 to 80/60, and the pulse rate increased from 65 to 144, as shown in the first section of Chart 3. The volume of the left lower leg increased by 475 cc within one minute upon release of a tourniquet which had been applied above the knee. The oxygen saturations of venous blood, taken simultaneously from one of the veins of the leg and from the antecubital vein, were 67 and 69 per cent, respectively.

At operation, the left long, and the right short, saphenous veins were ligated at the points where they pierced the deep fascia. After operation, the filling of the angiomata was delayed and the blood pressure no longer fell on standing, as shown in the second section of Chart 3. Further examination revealed additional points of incompetency.



FIG 1



FIG 2



FIG 3

FIG 1—Appearance of the feet in patient A E, 10 years after Doctor Gill had excised the epiphyseal cartilages of the metatarsal bones of both feet

FIG 2—Extensive angiomas and varicose veins on the lateral aspect of the thigh and leg in patient A E

FIG 3—Visualization of the veins of patient A E after injection of 30 cc of 30 per cent diodrast into the venous "lake" on the lateral aspect of the thigh

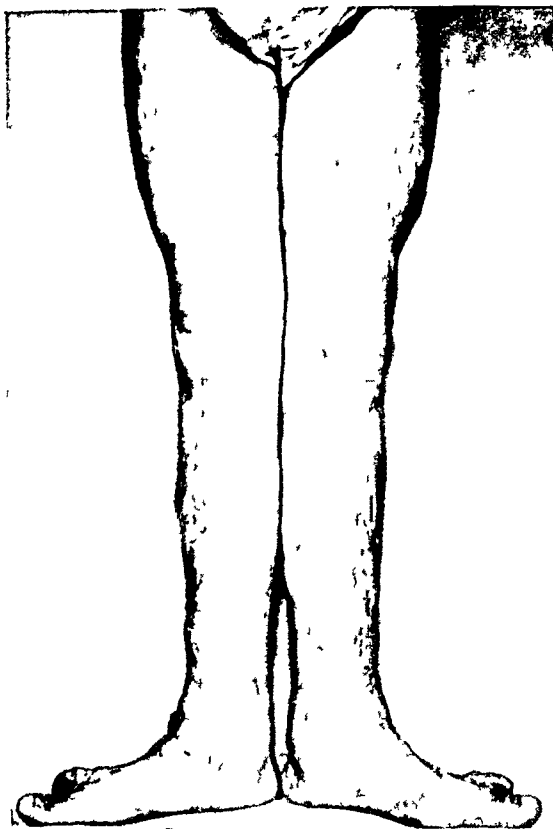


FIG 4—Appearance of the legs and feet of patient D O before ligation of veins

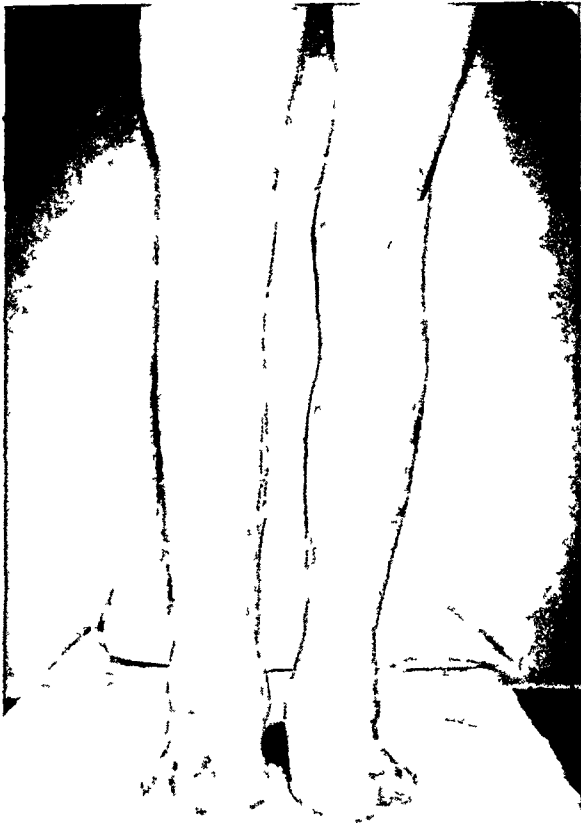


FIG 5—Appearance of the legs of patient D O after 30 seconds of standing after right short, and left long saphenous ligation

D O - Cavernous Hemangioma with Varicose Veins

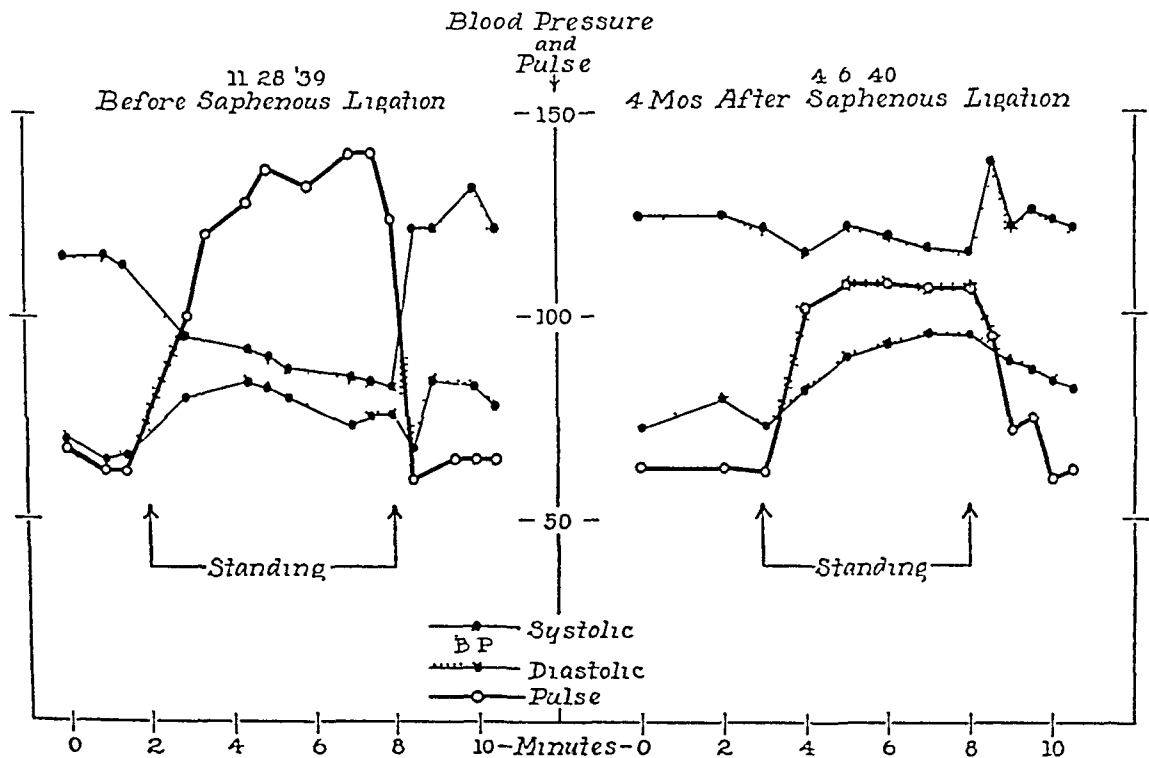


CHART 3—Effect of standing on blood pressure and pulse rate of patient D O before, and four months after, vein ligations

of the valves between the deep and superficial systems, in the region of the inferior gluteal on the right and in the mid thigh on the left side. The filling was slow, as the photograph taken after 30 seconds of standing after operation indicates, as shown in Figure 5. Ligation of these veins is now planned.

DISCUSSION—The essential difference between the condition which these patients presented and the cirroid aneurysm is the source of the filling. In the latter condition, there are abnormal connections of the angioma with the arterial side of the circulation. In the angioma of the lower extremity associated with varicose veins, the filling is from the venous side. It is only in the lower extremity that the venous pressure, in the absence of competent valves, is sufficiently high to produce expansion of the vascular bed. No case of angioma with varicose veins of the upper extremity has been observed. The fact that filling occurred from the venous rather than from the arterial side was indicated by the fact that there was no pulsation of the veins, and that the color and oxygen saturation of the venous blood taken from the affected extremities in two of our cases was identical with that taken from unaffected regions. An additional point of differentiation was the fact that filling could be prevented by the application of a venous tourniquet. If the angiomata had filled from the arterial side, the veins would have increased in size when a tourniquet obstructed the venous return. Finally, the reduction in size after ligation of the veins which communicated with the angiomata served as additional evidence of their venous character.

The presence of osteohypertrophy suggested a similarity between the angioma with varicose veins and the cirroid aneurysm since overgrowth of bone is constantly noted in the latter condition. The hypertrophy which was observed in the second and third cases, however, was spotty since all of the bones of the extremity were not involved. Again, in the patient who had only the angioma until she developed acute phlebitis, there was shortening of the affected extremity, similar to that described in Reid's¹⁸ patient.

The local symptoms in the first and third cases seemed to be due to the varicose condition, *i.e.*, swelling and discomfort. Klippel and Trenaunay⁵ comment upon the frequency with which varicose ulcers appeared in the cases which they reviewed. The outstanding symptom in our second case was pain. It is probably significant that this patient had repeated attacks of phlebitis in the superficial veins of the leg. Similar cases of pain in this condition were reported by Sorrel,⁸ in 1932, and Pautrier and Lang,¹² in 1937.

Reid¹⁹ was the first to call attention to the effects of the venous reflux on the systemic circulation. In his patient, the angioma was apparently not complicated by the presence of varicose veins. The blood pressure fell from 130/85 to 126/84, and the pulse rate increased from 86 to 116 on standing, but after ten minutes the pulse rate fell to 104. These figures are comparable to those obtained in all our patients after the main channels of reflux had been closed. The volume of blood lost from the general circulation into the angiomata was large. In the first patient, the increase in volume of the lower leg upon release of a tourniquet was 250 cc, and yet the more extensive part

of the angioma over the thigh and hip was above this region. In the third patient, the increase in volume of the left lower leg was 475 cc. The angioma extended up to the middle of the trunk on this side and the other leg was also involved. The increase in pulse rate, rise in diastolic and fall in systolic pressure may be compared to the physiologic effects of hemorrhage. As the return of blood to the right side of the heart diminished, there was a compensatory increase in pulse rate with vasoconstriction. The pulse pressure decreased both by a decrease in systolic blood pressure and a rise in diastolic pressure. Compensation for the impaired cardiac return was accomplished by these protective mechanisms. When the loss of circulating blood volume was too great, the cerebral tissues become anoxic and fainting occurred.

The venous valve is probably of major significance in the development of symptoms. In the two male patients certain valves which protected the superficial system from excessive pressure were absent or defective presumably on a congenital basis. The fact that the first patient suffered no ill effects until the valves had been damaged by phlebitis is in accord with this concept, since it has been shown by Edwards and Edwards²⁰ that the venous valve is destroyed during the process of recanalization after the thrombosis.

The usual treatment of this condition has been excision (Pautrier and Lang,¹² Kleinberg¹⁵ and DeTakats¹⁶), while injections were used by Light.²¹ Roentgenotherapy was considered useless for the superficial diffuse angiomas by Taylor.²² Homans²³ obtained permanent relief in his case by excision of the contributing vein at its head, and injections of sclerosing solutions into the peripheral portion. Reid¹⁸ stated "In my experience an extensive angioma involving the entire leg was cured, by thrombosis, after the excision of a very small portion of it." Since defective valves appear to be, etiologically, significant, rational treatment would appear to be ligation of the incompetent vein with subsequent sclerosis of the remaining segment if necessary. The progressive decrease in the capacity of the angiomas after the head of pressure was reduced in our cases, by ligation of the vein with the defective valve, may indicate that subsequent injections of sclerosing solutions will not be necessary.

BIBLIOGRAPHY

- ¹ Reid, Mont R. Abnormal Arteriovenous Communications, Acquired and Congenital. II. The Origin and Nature of Arteriovenous Aneurysms, Cirroid Aneurysms and Simple Angiomas. *Arch Surg*, 10, 996, 1925.
- ² Holman, E. Arteriovenous Aneurysms. New York, The Macmillan Co., 93, 1937.
- ³ Devouges, M. Predominance de Développement de Côte Droit sur le Côte Gauche. *Bull de la Soc Anat*, 31, 510, 1856.
- ⁴ Trelat, U., and Monod, A. De l'Hypertrophie Unilaterale Partielle ou Totale du Corps. *Arch Gen de Med*, 13, 536, 676, 1869.
- ⁵ Klippel, M., and Trenaunay, P. Du Naevus Variqueux Osteo-Hypertrophique. *Arch Gen de Méd*, 185, 641, 1900.
- ⁶ Van Neck, M. Gigantisme Partiel et Naevus. Naevus Variqueux Osteo-Hypertrophique. *Arch Provinciales de Chir*, 28, 599, 1925.

- ⁷ Pautrier, M L M, and Ullmo, A Hemangiectasis Hypertrophique de Parkes-Weber Bull Soc Franc de Dermat et Syph, 35, 981, 1928
- ⁸ Sorrel, E Angiome Diffus de Membre Inferieur Droit Bull et Mem Soc Nat Chir, 58, 758, 1932
- ⁹ Gougerot, H, and Lortat-Jacob, E Naevus Variqueux Osteo-Hypertrophique (de Klippel et Trenaunay) de Membre Inferieur Gauche Bull Soc Franc Derm et Syph, 41, 1668, 1934
- ¹⁰ Alajouanine, T, and Thurel, R Un Cas de Naevus Variqueux-Hypertrophique (Role de la Circulation dans la Physiologie de l'Os) Rev Neurol, 63, 719, 1935
- ¹¹ Radulesco, A D L'Hypertrophie Totale du Membre Inferieur avec Naevus Plan Vasculaire Osteosclerose Partielle et Acrocyanose J de Rad et D'Electrologie, 19, 575, 1935
- ¹² Pautrier, L M, and Lang, A Hemangiectasie Hypertrophique du Membre Inferieur Droit et du Scrotum, S'accompagnant D'hémolymphangiomes des Fesses Bull Soc Franc Derm et Syph, 44, 605, 1937
- ¹³ Touraine, A, Duperrat, R, and Baudouin, A Angiome Radiculaire, Caverneux et Verruqueux de Membre Inferieur Bull Soc Franc Derm et Syph, 45, 577, 1938
- ¹⁴ Homans, J Varicose Veins and Ulcer Methods of Diagnosis and Treatment Boston Med and Surg Jour, 187, 258, 1922
- ¹⁵ Kleinberg, S Angioma of the Leg ANNALS OF SURGERY, 91, 317, 1930
- ¹⁶ DeTakats, G Vascular Anomalies of the Extremities Surg, Gynec and Obstet, 55, 227, 1932
- ¹⁷ Wise, W D, and Lisansky, E T Congenital Arteriovenous Fistula or Fistulae ANNALS OF SURGERY, 108, 701, 1938
- ¹⁸ Reid, Mont R Abnormal Arteriovenous Communications, Acquired and Congenital III The Effects of Abnormal Arteriovenous Communications on the Heart, Blood Vessels and Other Structures Arch Surg, 11, 25, 1925
- ¹⁹ Reid, Mont R A Report of Vascular Lesions Am Jour Surg, 14, 17, 1931
- ²⁰ Edwards, E A, and Edwards, J E The Effect of Thrombophlebitis on the Venous Valve Surg, Gynec and Obstet, 65, 310, 1937
- ²¹ Light, S E The Injection Treatment of Cavernous Hemangiomas Arch Derm and Syph, 24, 992, 1931
- ²² Taylor, G W The Treatment of Hemangiomas at the Collis P Huntington Memorial Hospital Boston Med and Surg Jour, 195, 737, 1926
- ²³ Homans, J Personal communication

HEPARIN IN THE PREVENTION OF PERITONEAL ADHESIONS*

REPORT OF PROGRESS

EDWIN P LEHMAN, M D

AND

FLOYD BOYS, M D

CHARLOTTESVILLE, VA

FROM THE DEPARTMENT OF SURGERY AND GYNECOLOGY, UNIVERSITY OF VIRGINIA SCHOOL OF MEDICINE,
UNIVERSITY, VA

A PRELIMINARY REPORT,¹ recently presented, suggested that heparin, intra-abdominally administered, is effective in preventing the formation and reformation of peritoneal adhesions in the rabbit and dog. Ten dogs, receiving 3,000 units of heparin in solution in single daily administrations at operation and on each of two postoperative days, presented an adhesion reformation rate of 26 per cent, whereas the corresponding rate was 157 per cent in the control group of 20 animals, in which either no solution, normal saline solution, or amniotic fluid concentrate was administered intraperitoneally. In other words, after heparin the count of adhesions was about one-fourth of the count at the time of injection of the substance, in the control group the adhesion count showed more than half as many again at the final stage as compared to the number of adhesions divided †. Some doubts were expressed in regard to the safety of intraperitoneal heparinization from the point of view of hemorrhage on the basis of three fatal hemorrhages in 24 dogs. This high incidence of bleeding was believed to be the result of inadequate hemostasis at the time of dividing the adhesions.

The present report of progress offers evidence on three phases of the general study: (1) Intraperitoneal dosage, (2) the danger of hemorrhage, (3) the effect of intraperitoneal heparin in the freshly contaminated abdomen.

METHODS EMPLOYED—Dogs were employed throughout. The method for creating peritoneal adhesions was that used in the previous investigation.¹ Adhesions were consistently produced by perforating the appendix and smearing a small, measured quantity of its expressed contents over the terminal ileum and the adjacent cecum. In recent experiments, light, dry gauze scarification of the terminal ileum was an added technic preliminary to contamination. This procedure was found to localize the adhesions more successfully. The appendiceal perforations were not closed. Six weeks later the resulting

* Read before the American Surgical Association, St. Louis, Mo., May 1, 2, 3, 1940.

† Since publishing the original paper, five additional control animals were studied similarly with papain made up in Hartman's solution in a concentration of 1-20,000, as recommended by Ochsner.² The animals treated with papain presented a reformation of adhesions of 117 per cent. The results with papain were numerically the best of the control studies, bringing the average rate of adhesion reformation down to 147 per cent. The papain employed was obtained through the courtesy of Parke, Davis and Co. Detroit, Mich.

adhesions were divided and heparin solution in varying doses was administered intraperitoneally. In some animals (Table I) additional heparin was given by paracentesis on one or more subsequent days. A third operation was performed two weeks later, at which time the number of reformed adhesions was observed and recorded*. Powdered heparin was purchased from the Connaught Laboratories, at the University of Toronto, and was dissolved in sterile water at the time of use. Normal saline was originally employed as the vehicle but was discarded when the reformation results with saline solution alone were found to be the highest in the control series. A number of animals in these groups have been discarded on account of wound infections communicating with the peritoneal cavity as the result of an epidemic of contamination of the cages.

In the experiments dealing with the contaminated peritoneum, the heparin solution (3,000 units) was first introduced at the time of perforating the appendix rather than after adhesions had formed. Two additional doses were given by paracentesis on successive postoperative days.

RESULTS—Dosage Experiments Table I presents the results of the dosage experiments in which both the number of single daily administrations and the quantity of heparin per dose were varied. The figures indicate that more than two intraperitoneal doses are necessary, even when a relatively large number of units of heparin are administered, and that more than three doses do not improve the results. The number of reformed adhesions following two daily doses of 1,000 units each is appreciably greater than when 3,000 units are employed. When three administrations are made, the results of the 1,000 unit dose and the 3,000 unit dose are approximately equal.

TABLE I

REFORMATION OF ADHESIONS

Results Two Weeks Following Separation of Previously Produced Adhesions in the Dog After the Introduction of Heparin Solution Intraperitoneally by Paracentesis

Number of Dogs	Number of Daily Heparin Injections	Units of Heparin Given per Injection	Average Number of Adhesions Separated	Average Number of Adhesions Reformed	Average Per Cent of Adhesions Reformed
10	1	3,000	6.3	5.8	92
5	1	9,000	15.6	9.6	62
5	2	1,000	15.4	13.8	89
10	2	3,000	16.0	8.4	52
10	3	1,000	8.4	2.4	29
10	3	3,000	9.7	2.6	26
6	4	3,000	15.8	5.3	33

Hemorrhage—In experiments to date with intraperitoneal heparin administration, no further intra-abdominal hemorrhages have occurred. There

* The attempt at a quantitative method of recording results is, of course, inaccurate. It offers, however, the only objective method available short of direct observation of the animals.

have been to date 75 consecutive introductions of heparin without hemorrhage, and only three hemorrhages in a present total of 101 dogs

Heparin in the Contaminated Peritoneum—Table II presents the results of the introduction of heparin into the freshly contaminated peritoneum in 17 dogs as compared with the results in a group of 100 consecutive control animals in which the peritoneum was contaminated for the creation of adhesions for later study. Whereas 43 per cent of the control animals died of peritonitis, 53 per cent of the heparin dogs succumbed to this complication. In the animals that survived, however, the average number of adhesions formed in the heparin dogs was less than one-third of that formed in the controls.

TABLE II

HEPARIN AND CONTAMINATION

Results Following the Intraperitoneal Introduction of Heparin at the Time of Perforation of the Appendix

Group	Number of Dogs	Mortality Rate	Average Number of Adhesions in Living Dogs
No solution	100	43%	9.4
Heparin 3,000 units at operation and two additional doses	17	53%	2.9

DISCUSSION—The absolute figures furnished by the present experiments confirm the earlier conclusion that heparinization of the peritoneal exudate in dogs inhibits the reformation of divided intra-abdominal adhesions. The suggestion of a curve dependent upon dosage, as presented in Table I, adds further evidence of a definite heparin effect. To this may also be added the low numerical incidence of adhesions in the surviving dogs, presented in Table II.

The study of dosage is as yet incomplete. The method of attack is necessarily slow and final conclusions may be delayed. Furthermore, for reasons to be discussed below, the ultimate determination of the optimum dosage of heparin given intraperitoneally may not be pertinent. Certainly, for the moment, it is clear that more than two intraperitoneal doses are necessary, and that four daily doses do not present improved results over those following three daily doses. The minimum effective dose per day for three administrations has not yet been determined.

The freedom from further occurrence of hemorrhage has paralleled greater operative attention to hemostasis. It is probable, therefore, that the earlier explanation of the cause of the trouble at first encountered, namely, inaccurate hemostasis, is correct. We now feel that hemorrhage is not a danger, if bleeding can be completely controlled before introduction of the heparin solution.

In the earlier experiments with rabbits,¹ it was surprising that 100 per cent

of recoveries occurred when heparin was introduced into the peritoneum at the time of perforation of the appendix. It might have been expected that all such animals would die of general peritonitis on account of the assumed absence of fibinous adhesions. In the present group of dog experiments, almost equally surprising results occurred. It had been supposed that at least 90 per cent of the dogs in which heparin had been introduced at the time of perforation would die of peritonitis. In contrast to this expectation, only 53 per cent died, a mortality not strikingly different from that among the controls. This seems to indicate that heparin may not materially increase the danger of peritonitis when the peritoneum is soiled. We are not yet ready to suggest a modification of the traditionally accepted ideas of peritoneal defense against infection as at least partially effected through fibrinous adhesion about the source of contamination. We feel, however, that these results indicate the possible usefulness of heparin in the contaminated peritoneum provided the source of contamination is not still present, as for instance following intestinal suture. Further experiments in this connection are contemplated.

The studies so far prosecuted do not yet permit of clinical application. We are convinced of the effectiveness of heparin and of its safety. The method of administration and the optimum dosage are still undetermined. It must be pointed out that repeated daily intraperitoneal administration is not well adapted to clinical use. Postoperative paracentesis in patients may be uncomfortable and may present danger. Three other methods of administration are now under investigation. (1) The first is based on the possibility that an intraperitoneal exudate may be uncoagulable if the blood plasma from which it is derived is first rendered relatively uncoagulable by subcutaneous or intravenous heparinization. In these studies heparinization of the animal is begun by these routes as soon as the operation for division of adhesions is completed. (2) The second method combines intraperitoneal administration of heparin at the time of division of adhesions (as in the present experiments) with subcutaneous or intravenous heparinization in an attempt to prolong the local effect. (3) The third attack is a study of intraperitoneal drip heparin administration through an indwelling rubber tube introduced at operation.

Until the best method has been worked out in the dog application to the clinical case must be delayed. As stated in the earlier report the possible success of the method in clinical surgery must, at least for a long period, be judged on laboratory rather than clinical evidence.

CONCLUSIONS

(1) Intraperitoneal heparinization in three daily doses of at least 1,000 units largely prevents the reformation of divided peritoneal adhesions in the dog.

(2) Hemorrhage following the intraperitoneal administration of heparin is not a danger if hemostasis is complete before the heparin is administered.

(3) Contamination of the peritoneum does not appear to be a contraindication to the intraperitoneal use of heparin

REFERENCES

- ¹ Lehman, Edwin P., and Boys, Floyd The Prevention of Peritoneal Adhesions with Heparin An Experimental Study ANNALS OF SURGERY, III, 427-437, March, 1940
² Ochsner, Alton Personal communication

DISCUSSION—DR HARVEY B. STONE (Baltimore, Md.) Every general surgeon, I think, must be greatly interested in any proposed method of diminishing abdominal adhesions and I personally have been particularly interested in this because, many years ago, one of the earliest pieces of experimental work that I undertook concerned itself with measures designed to prevent adhesions—and I might say in passing, it was completely unsuccessful. So when Doctor Lehman's work came to my attention, naturally, I was immensely interested in it, because it seemed to me that it was the most logical and hopeful attack on the problem that I had personally ever heard of.

The purpose of my speaking at all now is to report very briefly some uncompleted work which is being carried on by Doctors Owings and Hewitt, two of the younger men connected with the Hopkins Clinic, which they have given me permission to speak about. They are working on the same issue, namely, heparin as a preventive of abdominal adhesions, but have purposely modified, in several directions, the technic employed by Doctor Lehman, in order to explore varieties of procedure which may increase the success of the method. They have used various means of inducing adhesions, and the one, at the moment, which they have found most effective and, in their judgment at least, most suitable for comparative studies, is the production of a chemical irritation by painting of serous surfaces with small amounts of ferric chloride. Their experimental animals have been cats instead of either dogs or rabbits. They have used a different preparation of heparin, or at least heparin from a different source from that employed by Doctor Lehman, so that from many aspects of detail, their series will give a comparable study to his. Their work is by no means completed, in fact, I am requested to say that they are not in a position to express any opinion as yet about the results but merely to say what they have done.

First, I might say they have had no hemorrhages at all in their series of animals as a result of the introduction of heparin. They have found, beginning with smaller doses than those employed by Doctor Lehman, for instance, a considerable series in which 250 units of heparin were employed, no recognizable benefit. They then increased the dose of heparin to 500 units, again with no demonstrable reduction in the amount or extent of adhesions. However, in a third series in which 1,000 units of heparin were employed as an initial dose and two successive similar doses given each succeeding day, so that in all, the dog received 3,000 units intraperitoneally, they have obtained a beginning promise of result. Now, it will be noted that only in this last series is their dose at all comparable to the amount employed by Doctor Lehman in his very promising work. So that their first statement is, so far as they have gone, these smaller doses are ineffective.

They have reexplored one-half of their current series of cats in which three successive doses of 1,000 units have been employed, and out of a series of eight animals so explored, one showed notable reduction or absence in the amount of adhesions discovered at the second exploration. Now, that is as far as they are prepared to make any statement, and obviously no generaliza-

tions can be made from such fragmentary facts, nevertheless the work is so important, if successful, and so promising in theory, that we expect to go on with it, exploring different modifications, and we hope that Doctor Lehman has at last found a really effective solution of the troublesome problem of adhesions

DR J ALBERT KEY (St Louis, Mo) I would expect that if heparin were present in sufficient amounts to prevent formation of fibrin, there would be some delay and difficulty in the healing of the wound and I would like to know whether that has been noted

DR EDWIN P LEHMAN (University, Va, closing) The problem of wound hemorrhage following the use of heparin, which Doctor Key has inquired about, was, of course, in our minds The experience of those who have used heparin extensively in vascular surgery, both in the laboratory and in the human being, has been that there has been no trouble with this complication With intraperitoneal administration of heparin the animals showed a definite prolongation of the coagulation time, which lasted about 12 to 18 hours The coagulation time is increased from a normal of three minutes to a maximum of about 12 minutes In none of them did we have wound hemorrhage, or any disturbance of healing which could be attributed to bleeding

EDITORIAL ADDRESS

Original typed manuscripts and illustrations submitted to this Journal should be forwarded prepaid, at the author's risk, to the Chairman of the Editorial Board of the ANNALS OF SURGERY

Walter Estell Lee, M D
1833 Pine Street, Philadelphia, Pa

Contributions in a foreign language when accepted will be translated and published in English

Exchanges and Books for Review should be sent to James T Pilcher, M D, Managing Editor, 121 Gates Avenue, Brooklyn, N Y

Subscriptions, advertising and all business communications should be addressed

ANNALS OF SURGERY
227 South Sixth Street Philadelphia, Pa

BRIEF COMMUNICATION

A DURALUMINUM ENTEROTOME FOR DEVINE COLOSTOMY

MIMS GAGE, M D

NEW ORLEANS, LA

FROM THE DEPARTMENT OF SURGERY, SCHOOL OF MEDICINE, TULANE UNIVERSITY, NEW ORLEANS, LA

It is hardly possible to devise or modify an instrument without incorporating some of the principles of preexisting instruments as well as maintaining the contour and general shape of the instrument to be modified

The need for modifications depends upon some demonstrable defect found at the time the instrument is used. In applying one of the modified Devine clamps to a colostomy it was found that the central opening of the clamp was too small to surround the "abdominal wall bridge" between the two colostomy openings. This produced some squeezing of the "abdominal wall bridge" which resulted in considerable discomfort to the patient. It was predictable that as the abdominal wall increased in thickness, the pressure on the intercolostomy bridge of the abdominal wall would increase.

To overcome this defect it was necessary to increase the total diameter of the central opening of the clamp that encompassed the "abdominal wall bridge." To accomplish this, it was important to use a metal that would be light in weight, of considerable tensile strength, and durable. Duraluminum was found to be such an ideal metal—meeting all the requirements noted above. Therefore, the instrument was made of duraluminum of 0.5 cm thickness and chromium plated. The instrument, as shown in Figure 1, is a modification and adaptation of the Cook's pile clamp to the requirements of the Devine colostomy clamp.*

The clamp is only 17 cm in length, therefore, the two handles (Fig 1, D and C) protrude for only 6 cm above the surrounding skin surface. The central opening, which encompasses the "abdominal wall bridge" between the two colostomy openings, is 5 cm in the transverse and 4 cm in the perpendicular diameters. Therefore, the opening will accommodate the abdominal

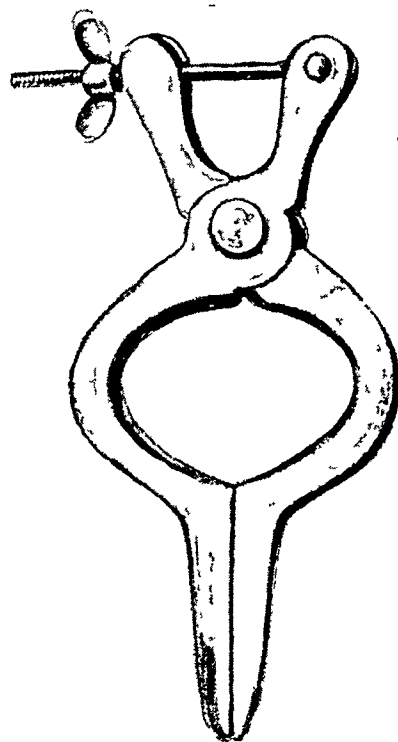


FIG 1A—Enterotome for Devine colostomy. Closed position

Submitted for publication August 18, 1939

* The instrument is manufactured by V. Mueller and Co. of Chicago, Ill.

wall intercolostomy bridge in either the obese or slender patient without difficulty or discomfort. The blades of the clamp (Fig 1 A and B) are 5.5 cm long and have an interlocking, serrated edge on the crushing side of the blade. The two limbs of the clamp interlock and are held together by a lock screw (Fig 1 E). The blades are pulled together to produce the crushing of the interposed septum by the bolt and wing nut (Fig 1 D).

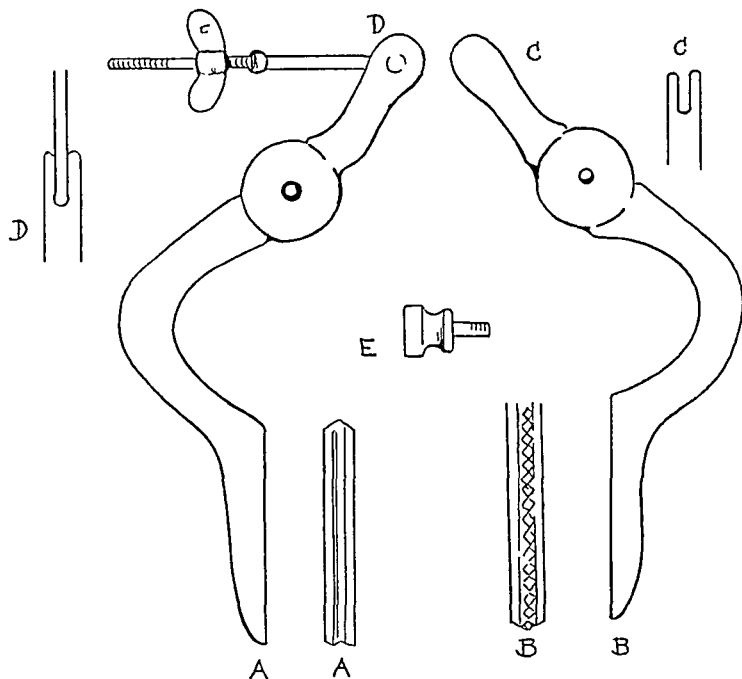


FIG 1B—(A) Closed position (B) Disassembled, showing the component parts

The application of the instrument to the colostomy is very simple. The blades of the clamp are separated by removing the lock screw (Fig 1 E) and disengaging the bolt (Fig 1 F). One blade is inserted into the distal limb of the colostomy. With the forefinger in the proximal limb, the blade is placed in the correct position. The finger is removed and the other blade is introduced into the proximal limb, the two handles are engaged, and the thumb-lock screw (E) is put in place and screwed up tightly. The cross bar (D) is replaced and the wing nut tightened sufficiently to coapt the blades snugly against the colocolon septum. The wing-screw is tightened daily one-half to one full turn until the seventh or eighth day, at which time, by ischemic necrosis, the septum is crushed through. When the spur has been severed, feces exude through the distal colostomy opening.

ERRATA

In the article appearing in *ANNALS OF SURGERY*, 112, 240-248, August, 1940, on "Plasma Transfusion in Experimental Intestinal Obstruction" by Doctors Jacob Fine and Samuel Gendel, two errors have occurred. (1) Page 247, the word "for" in the second sentence of the third paragraph, should be "to", and (2), in the first line of page 248, the figure "208" should be "20 8".



CARCINOMA OF THE THYROID

FRANK H LAHEY, M D ,

DEPARTMENT OF SURGERY,

HUGH F HARE, M D ,

DEPARTMENT OF RADIOLOGY,

THE LAHEY CLINIC,

AND

SHIELDS WARREN, M D *

BOSTON, MASS

"IN THE ADVANCED STAGES of carcinoma and sarcoma we cannot control the growth of the thyroid. Extirpation of the diseased substance will alone cure the patient from its ravages, but this can only be undertaken in the early stages of the complaint." Thus spoke Allan Burns,⁴ in 1811, regarding cases of cancer of the thyroid which he had seen, but he did not mention total extirpation having been performed.

In 1822, Chetums⁷ gave a short but admirable description of the struma scirrhusa. He emphasized the knobby, hard consistency, the strong boring pain, the dyspnea and asphyxia, diffusion with neighboring structures especially the trachea, muscles of the neck, and he closed with the statement "Finally it is transformed into a carcinoma, a true cancerous growth in which the neighboring nodes of the neck enlarge."

In 1855, Billroth² reported a case of thyroid tumor with associated enlargement of the lymph nodes which showed the same variation in morphology as did the thyroid tumor. Billroth was the first to speak of any treatment other than surgery for this condition. He attempted to employ electrocautery by puncture and believed that his patients received symptomatic relief for several days. He was the first to comment on the presence of fetal thyroid disease and goiter.

Cohnheim,¹⁰ in 1876, made one of the first histologic subdivisions for thyroid cancer, and at this time noticed that some of the thyroid cancers resembled closely the normal gland, he used the term "benign metastasizing goiter." Criticism of this term was started by Wolfier,²⁵ in 1883, and continued until the time of Graham's work, published 50 years later.

Wolfier, in 1883, gave a very clear-cut pathologic classification of thyroid

* Pathologist, New England Hospital and Palmer Memorial Hospital, Boston, Mass.
Submitted for publication December 11, 1939

cancers similar to that in use to-day. He stated at that time that a typical vascularization is a probable factor in the production of thyroid cancer. The thyroid tissue retains its fetal characteristics until old age and commonly gives rise to atypical epithelium and proliferation of epithelium more than normal tissue. Embryonal masses of epithelium are usually found in the thyroid and, more commonly, in goiters. In these cases he assumed that carcinoma develops if the vascularization either remains atypical or becomes atypical as a result of hemorrhage or venous hyperemia.

In 1902, Ehrhardt¹¹ reported 200 cases of carcinoma of the thyroid, from which he attempted to draw several conclusions. He stated that in 104 cases a preexisting adenoma was present. In only 21 cases could a preexisting goiter be proved. He believed that degenerative changes, notoriously frequent in old goiters, act as chronic trauma since atypical epithelial growth has been observed in the vicinity of these degenerative changes. This change may be the anatomic expression of the clinically proved relationship between goiter and malignant thyroid.

In 1905, Bloodgood³ stated there is little or no hope in carcinoma of the thyroid if the operation is performed when the tumor has reached a stage when a clinical diagnosis can be made. Malignant tumors of the thyroid must be removed in the early stage, a period in their growth when they cannot be differentiated from a benign cyst and adenomata. For this reason, every asymmetrical enlargement of the thyroid gland in individuals over 30 years of age should be removed.

Thus, until the twentieth century, time was spent in developing a suitable pathologic classification but rarely was an attempt made to remove these tumors surgically. Enough clinical material had been gathered by 1921 for Wilson²⁴ to report 21 authenticated cases studied in the United States. He considered that any adenoma of the thyroid composed of embryonal tissue giving histologic evidence of active proliferation is potentially malignant even though it is still contained entirely within the capsule. Wilson was the first to report the results of treatment in 207 cases in which operation alone was performed. Of these 207 cases, 194 were followed and only nine patients lived five or more years after operation.

One of the most useful contributions to our understanding of malignancy of the thyroid gland is the significance of blood vessel invasion, as pointed out by Allen Graham,¹⁴ in 1925. This explained once and for all the paradox of benign metastasizing goiter and also gave for the first time a fairly satisfactory means for selection of those cases which are either actually or potentially malignant and those which are entirely benign. This criterion is not hard and fast, however, as definite blood vessel invasion is found at operation in a number of cases in which no metastasis is found.

The subject of cancer of the thyroid is one that urgently deserves attention, not only on the part of the medical profession, but also by the laity. It deserves this attention and interest because, as will be seen in this discussion, it so often exists first as a benign tumor later becoming malignant, because its removal at this stage or even in an early stage of malignant degeneration

offers such an excellent chance or even possible cure after malignant degeneration has occurred. While the knowledge that many carcinomata of the thyroid originate in discrete adenomata has been repeatedly stressed and is appreciated by a great many physicians, there are still many who either do not realize the possibilities of prevention of carcinoma of the thyroid by removal of these adenomata before they have become malignant, or are not so impressively convinced of this danger that they are willing to advise early prophylactic removal of these tumors. This subject, likewise, deserves attention because there still exists in many physicians' minds an attitude toward this subject which was present, and perhaps justifiable, some years ago but not now—that is, that all cancers of the thyroid were quite hopeless from the point of view of cure.

It is not surprising that individual opinions on this subject should be what they so often are because of the fact that cancer of the thyroid occurs in such a small percentage of patients with goiter that in any individual's practice, unless it be one dealing with patients with goiter in large numbers, an insufficient number of cases will occur to permit him, by actual experience, to obtain information and convictions about the true state of this situation. It is because of the fact that we have had the opportunity of having performed 18,600 goiter operations, and so having had the opportunity to see and manage such a considerable number of patients with malignancy of the thyroid, that we feel obligated to present our experiences with the subject. Since a series of reported cases from a clinic such as ours represents the experiences and results of the combined efforts of surgeons, roentgenologists and pathologists working closely together on cases which have been carefully followed, it permits deductions to be drawn from these not inconsiderable data, the justification of which may be settled and applied to each reader's personal experience with malignancies of the thyroid.

The logical approach to decreasing the number of patients who lose their life from malignancy arising in any given organ is above any other consideration concerned with the removal of premalignant lesions in that organ when such states are known to exist. It seems worth while, therefore, to cite briefly a few illustrative histories out of a large number of malignant degenerations in adenomata which have existed for a considerable period of time without evidences of malignancy. In these cases, it can with quite reasonable safety be stated that for at least a definite period of time the adenomata were not malignant and their removal during this period would quite probably have resulted in the prevention of malignancy.

ILLUSTRATIVE CASE REPORTS

Case 1—A female, age 20, came to the clinic June 23, 1937, because of enlargement of the neck for the past three or four years. It had been known to her medical advisers that this enlargement was due to a palpable, discrete adenoma of the thyroid. She had been advised that since it had given her no trouble it should not be removed.

Examination revealed a very moderate smooth enlargement of both lobes of the thyroid gland. A firm, smooth, round adenoma the size of an English walnut could be felt in the left lower pole extending beneath the sternum. Roentgenograms of the

trachea showed a soft tissue mass to the left and anterior to the trachea, displacing it to the right and compressing it anteroposteriorly. It is to be noted that this patient and her physicians knew that she had had this adenoma for three years but she had been wrongly advised to do nothing about it until it bothered her.

On June 25, 1937, partial thyroidectomy and wide removal of the adenoma were performed. The pathologist's report was carcinoma, partly papillary, partly small cell type. The patient was discharged July 23, 1937.

Roentgenotherapy was begun July 6. A series of 23 treatments was given, 7,000 r units were delivered to the thyroid region. There was an extremely severe postradiation reaction to combat, in which quite aggressive measures were necessary.

The patient married and remained well until March, 1939. She returned March 24, 1939, because of headaches for the previous three weeks. The headaches were frontal in type and came on at any time of the day or night. She had had no difficulty with the neck. There was no sign of local recurrence and her general condition was quite satisfactory. Roentgenograms of the accessory sinuses showed them to be well developed and apparently clear.

On May 1, 1939, right cerebral craniotomy was performed by Doctor Horrax of the Neurosurgical Section in the clinic, with excision of a suspicious area in the post-frontal region, decompression for extreme edema and removal of bone flap. The diagnosis was metastasis from the thyroid carcinoma. The patient died May 17, 1939.

Without intending to be specifically critical of her medical advisers but solely for the purpose of presenting the case as a lesson, the deduction from this history is sad but clear and unmistakable. Had this young lady had her small adenoma of the thyroid removed three years previously when it first appeared she would in all probability be alive and well to-day.

Case 2—A male, age 24, came to the clinic January 31, 1935, because of a "goiter" of ten months' duration. There had been little or no change in the size of the neck during this period. No symptoms were present and the patient felt physically fit.

Examination revealed the left lobe and isthmus of the thyroid gland to be enlarged to four times normal size by the presence of a discrete, movable thyroid adenoma. The trachea was deviated to the right in the lower cervical region. Since there was no hyperthyroidism present in this case it was with difficulty that this young man and his parents were persuaded regarding the wisdom of removing it. It was only when the general danger of malignancy in all thyroid adenomata was stressed that operation was even considered. This patient strenuously resisted immediate operation because of a desire to complete an already begun important year of graduate study.

On February 11, 1935, a discrete adenoma, approximately 6.5 cm in diameter, was removed from the left lobe. The pathologist's diagnosis was papillary adenocarcinoma. The patient was discharged February 16, 1935.

A series of 12 roentgen ray treatments were given, directed to both sides of the neck through two portals.

The patient has remained well to date and there is no evidence of recurrence.

In this case there is also a lesson. Had this patient had his adenoma removed ten months previous to the time when he did he might well have escaped malignancy. Had he been permitted to complete his year of graduate study he might well have lost his life.

Case 3—A female, age 31, came to the clinic January 30, 1935, because of swelling of the neck for two years. Examination revealed two discrete adenomata the size of English walnuts in the upper pole of the right lobe and a single small adenoma in the left lobe. This patient and her husband were strongly opposed to any operative procedure. The thyroid tumors were not of sufficient size to make them visible. They

caused no pressure. There was no toxicity and they had been advised against removal by their attending medical adviser.

At operation, February 6, 1935, two adenomata of the right lobe were found and the lobe was enlarged one and one-half times its normal size. There was a single adenoma in the upper pole of the left lobe. A right subtotal hemithyroidectomy with removal of the adenomata and excision of the adenoma of the left lobe was performed. The pathologic diagnosis was papillary adenocarcinoma. She was discharged February 15, 1935.

A series of 11 roentgen ray treatments, of 300 r each, was given, delivered through two portals. A fairly marked skin reaction occurred following the treatments.

The patient has remained well and there is no evidence of recurrence.

Again, in this case, this patient had been assured repeatedly that the enlargement in her thyroid was harmless and did not require attention. It was only when the aid of her uncle, who was a physician, was enlisted that she could be persuaded to have the operation performed. No one can deny the fact that the removal of these adenomata two years earlier would have been wiser.

Case 4—A female, age 67, first came to the clinic with her attending surgeon because of a disagreement on the part of her physician and her surgeon as to whether or not she should be operated upon for possible gallstones. It had been known for some years that she had a discrete adenoma of the thyroid. After examination at the clinic, it was advised and accepted that she did not have gallbladder disease and should not have any operation for it, but removal of the adenoma in her thyroid gland was strongly advised. While her physician and her surgeon were divided in their opinion concerning operation upon her for gallstones they were positively united in opposing any operation upon a single adenoma of the thyroid which had been present without symptoms for many years, and it was only when the responsibility for possible, though unsuspected, carcinoma was placed upon the patient and her physician and surgeon that it was accepted.

This unruptured adenoma was removed, it was considerably substernal. The pathologist's report was adenocarcinoma. Roentgenotherapy was given to the region of the thyroid gland.

While the patient has remained well, it, undoubtedly, would have been better to have removed this adenoma as a prophylactic measure earlier, and had further delay resulted an unnecessary fatality would undoubtedly have occurred.

These typical examples represent but a few of a large number of our cases of malignancy of the thyroid in which, from the history and the pathologic findings, it could be assumed that a benign adenoma of the thyroid had been present for some time, the removal of which, in this stage, would have permitted the individual to have escaped the resulting risk to his life and intensive postoperative radiation, with its necessarily associated roentgen ray sickness and the unavoidable and disfiguring skin changes associated with massive high voltage roentgen radiation. Numerous examples similar to the first case, in which it can be reasonably assumed that the patient lost her life needlessly, occur in our records and could be reported in considerable numbers but would serve no purpose other than to undesirably present criticism of the lack of knowledge concerning malignant changes in adenomata of the thyroid on the part of patients and their advisers.

CLINICAL DIAGNOSIS OF MALIGNANCY OF THE THYROID—While it will

be impossible in many cases without biopsy to settle with certainty the absolute presence of malignancy and its type, which is of particular importance from the point of view of prognosis and the justification of prolonged and intense roentgenotherapy, it will be of value to discuss from the point of view of a surgeon who has examined many of these cases preoperatively the features which suggest the possible presence of malignancy in the thyroid and the conditions with which they may be confused

The thyroid state which will most often cause the observer, with but little experience in palpating thyroid glands, to consider wrongly the possible presence of malignancy of the thyroid is that of thyroiditis. When the thyroid gland is chronically inflamed and occupied by round cell infiltration, as it is in this state, it assumes such a condition of stony hardness as to resemble that condition which one sees so frequently associated with malignancy anywhere and particularly in the thyroid. The distinguishing diagnostic point about thyroiditis as compared with carcinoma of the thyroid is that it is a diffusely infiltrating process, pervading the entire gland or one lobe of the gland and causing but moderate and symmetrical general enlargement.

The outstanding clinical diagnostic feature of thyroiditis is that while the gland may take on a hardness of almost marble-like consistency its symmetry and anatomic outline remain in general unchanged. This is quite in contradistinction to what one finds in malignancy of the thyroid. Since malignancy of the thyroid usually arises first locally, the symmetry of the gland is frequently lost. Local enlargement of the gland occurs and distinguishable firmness in the palpated lesion usually does not occur until the malignancy is quite well advanced. The association of enlarged adjacent cervical lymph nodes with any indurated swelling of the thyroid should make one very suspicious of thyroid malignancy.

The feature indicating possible malignant degeneration of an adenoma of the thyroid, which has existed for some time, is a change in consistency from one of moderate firmness to one of induration. The two common causes of a change in consistency to one of unusual firmness in an adenoma of the thyroid are the occurrence of malignant degeneration within the adenoma and hemorrhage into the adenoma. The former occurs gradually and without pain and localized tenderness. The latter occurs in a quite short period of time and is usually associated with pain and localized tenderness in the adenoma. When in a discrete adenoma or adenomata, which have existed for some time with well defined and palpable outlines, a loss of this sharply defined outline with diffusion of the firm tumor mass into the parenchyma of the gland occurs, one should be suspicious that malignant degeneration has taken place inside the adenoma, eroding through the capsule, involving the parenchyma and so causing to be lost the discrete outline of the unruptured discrete thyroid adenoma (Fig 1). When a discrete adenoma or discrete adenomata of the thyroid have existed for some time as quite movable tumors, and have then become fixed to the surrounding structures, one should be suspicious that this fixation is caused by malignant degeneration within the adenoma, erosion of the capsule and invasion of adjacent tissues, thus

causing the fixation. While the reactions about a thyroid adenoma secondary to hemorrhage into the tumor produce some degree of fixation, this is far less definite than is the fixation caused by malignant degeneration within the adenoma. The firm attachment of the prethyroid muscles to any firm tumor felt at the time of operation is extremely suspicious evidence of the probability that the firmness and the attachment of the thyroid tumor to the muscles are the result of malignant degeneration within the adenoma. When at operation, with the separation of the prethyroid muscles from the anterior surface of an indurated thyroid gland, bits of the thyroid come away from the in-

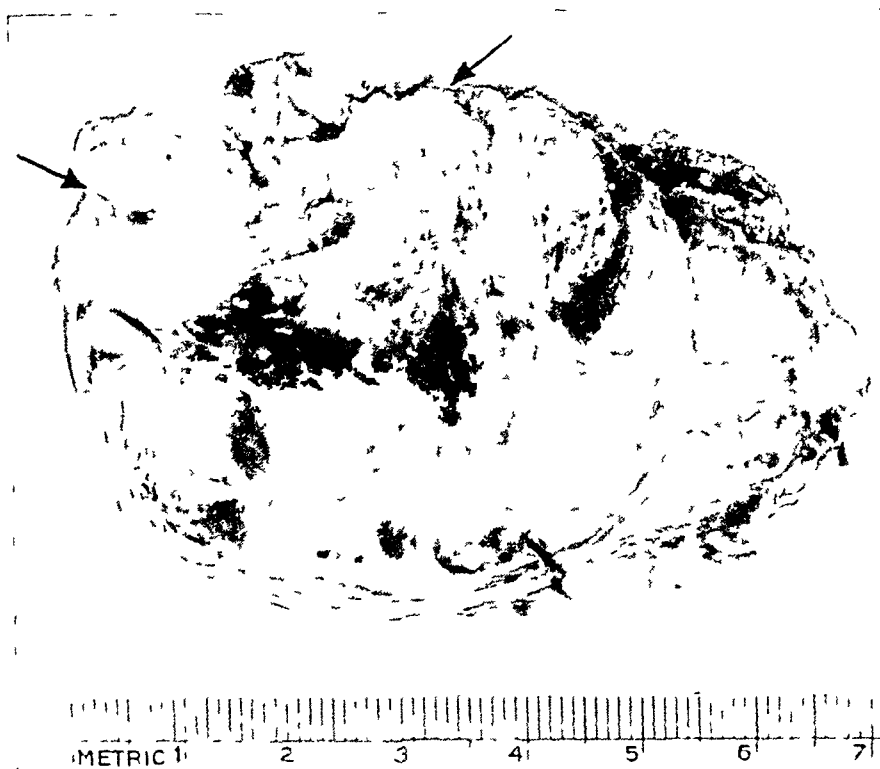


FIG 1—Adenoma of the thyroid with malignant change showing erosion of the capsule

durated gland adherent to the muscles, this is quite suggestive evidence that the lesion is malignant and has already infiltrated into these muscles. Voice changes due to recurrent laryngeal paralysis secondary to involvement of the nerve in malignancy occasionally occur, but extensive malignancy of the thyroid can so often occur without producing this paralysis that this feature has but little value as a sign indicating the possible presence of malignancy in the thyroid.

Up to the time that we had had a considerable experience with malignant degeneration in adenoma of the thyroid, we had assumed two attitudes which we now know were not proper ones. One was that there was little likelihood that malignant degeneration would occur in a very small thyroid adenoma and the other, that there was but little, if any danger of a thyroid adenoma becoming malignant in a young person. In Figure 2 may be seen an adenocarcinoma occurring in an adenoma the size of one's thumbnail, and this has occurred several times in our experience. Malignancy of the thyroid has

now occurred in our experience in so many young people that we know that dependence upon youthfulness in patients with adenomata of the thyroid as a protection against possible malignant degenerations is not advisable

While there is a lack of appreciation and aggressive surgical action in the matter of malignant degeneration in adenomata of the thyroid, there is also an almost universal lack of knowledge in the minds of most physicians and many surgeons concerning the existence of, the diagnostic features of, and the proper management of the sometimes already malignant and in all cases potentially malignant lesions associated with the occurrence of lateral aberrant thyroid masses

The thyroid gland in intra-uterine life arises at a point in the fetus, indicated in later life by the foramen caecum, at the apex of the circumvalate papillae on the back of the tongue

It is at this point at which the thyroglossal duct, then connected with the thyroid, empties. With increase in size of the fetus, the thyroid gland descends from its place on the back of the tongue to its position on the tracheal rings, leaving along its course of descent the thyroglossal tract which normally becomes completely obliterated. When failure of obliteration occurs a thyroglossal cyst is then formed. Occasionally thyroids fail to descend into their position in the neck and then the so-called lingual thy-

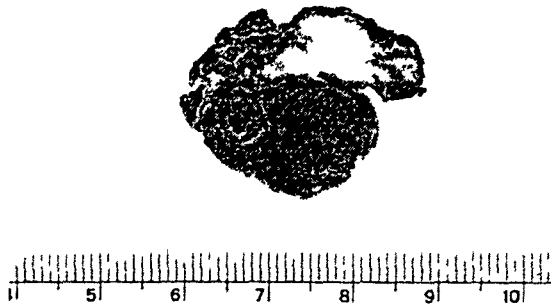


FIG 2—Portion of the thyroid with a small adenoma in which adenocarcinoma is present

roid occurs, three examples of which we have had in our experience

While the true origin of the thyroid is from this central anlage, there occasionally arise laterally from one or both sides of the neck papilliferous glandular masses from the ultimobranchial bodies which are known as lateral aberrant thyroids. These aberrant thyroid structures occur up and down the neck just in front of and under the edge of the sternocleidomastoid muscle. They are discrete, gland-like masses varying in size and consistency with the length of time which they have existed. In their early stage, they closely resemble enlarged lymph nodes and are often mistaken for them. They are in the beginning soft, freely movable and discrete, and do not tend to mat together. They cause no symptoms whatever when they first appear and are often thought by those who have not had experience with them to be inflamed cervical lymph nodes. These lateral aberrant thyroid masses frequently occur with a coexisting similar papilliferous nodule within the thyroid gland itself which may represent a metastasis of these lateral thyroid bodies into the thyroid gland. This situation can and has led to the removal of one of the gland-like masses or the nodule in the thyroid and its submission to a patholo-

gist If it be one of the lateral gland-like structures and the report that comes back from a pathologist is simply malignancy without qualification, the assumption has been, in cases operated upon elsewhere and with which we have dealt, that the tumor in the thyroid is malignant and the lateral gland-like masses in the neck are metastases. If the tumor in the thyroid is removed first and this pathologic report is returned, then the same improper interpretation of the situation can occur. Both of these experiences have occurred in our practice in patients later sent to us for operation, when the true state of affairs had been settled. It is important to realize the necessity of complete dissection of both sides of the neck, together with wide removal of any tumors within the thyroid itself, when these lateral aberrant thyroid bodies exist.

In such a situation as is above described, we have had patients sent to us in whom upon removal elsewhere of the papilliferous nodule in the thyroid and a report of malignancy of the thyroid returned, without specifying the type by a pathologist without considerable experience with thyroid disease, it was assumed that what in reality were lateral aberrant thyroid bodies were metastases to the lymph nodes and that the case was hopeless. In such cases it has been assumed that further operative procedures were not indicated because of the hopelessness of the situation in view of the metastatic nodules in the lymph nodes.

Such a situation would, of course, never occur in the hands of a surgeon or a pathologist who had had any considerable experience with thyroid states. It does, and has, in our experience occurred several times in the hands of men who have not had considerable thyroid experience, and with no purpose of criticism but rather to impress upon all the need to have in mind the possible presence of the lateral aberrant thyroid bodies and their potential malignancy, it is cited. To give patients, having these lateral aberrant thyroid masses with or without thyroid implantations, the best chance both sides of the neck should be thoroughly dissected from the clavicles to the mastoids with complete removal of all aberrant thyroid tissue together with any nodules in the thyroid gland itself. We have had 36 cases of malignancy of the lateral aberrant thyroid bodies in which operation was performed, and two patients have died of recurrence.

The most satisfactory management of thyroid malignancy to-day is by means of a combination of radiation and surgery, as is shown in Table I by

TABLE I
CARCINOMA OF THE THYROID
Five-Year Survival Rate 231 Cases

	Per Cent
Adenoma with blood vessel invasion	71
Papillary cystadenoma malignant	62
Papillary adenocarcinoma	80
Alveolar adenocarcinoma	27
Small cell carcinoma	22
Giant cell carcinoma	17
Fibrosarcoma	33

the five-year survival figures in patients treated by surgery and radiation. Surgery finds its most satisfactory place, of course. First in the prophylactic removal, while the tumor is still benign, of the discrete tumors of the thyroid in which malignancy may later arise. It finds its next most satisfactory application in those tumors in which malignancy exists within the capsule of such an adenoma but without erosion or invasion of the capsule. Its next most satisfactory application is in those cases in which malignancy has occurred within the adenoma, has eroded the capsule and involved the parenchyma of the thyroid at only one point, so that relatively complete removal of the malignancy can be accomplished. Its least satisfactory application will, of course, be in those cases with wide infiltration of muscle, trachea and lymph nodes by the infiltrating thyroid growth.

As the result of this quite extensive operative experience with thyroid malignancy, we have, with our successes and failures, acquired quite definite convictions concerning the employment of surgery in thyroid malignancy.

We believe that it is wise, even in advanced thyroid malignancies, to obtain a biopsy specimen for pathologic examination, since the degree of radiosensitivity is known to vary so much with the different types of thyroid carcinoma. We have as have many other men interested in thyroid malignancy, had cases with extensive and seemingly hopeless thyroid malignancy which when of the radiosensitive type, under radiation, have become discrete, movable and removable. We have seen their metastases controlled by radiation and have seen them with repeated radiation and local removal live many years, to die of entirely other causes than their thyroid malignancy. One of many examples is the case of a woman who recently died here of coronary thrombosis. Seven and one-half years ago she appeared in the clinic with extensive, seemingly hopeless, malignant papillary cystadenoma of the thyroid, with multiple fixed masses and metastasis to the cervical lymph nodes. Under radiation these masses became mobile and discrete, were removed, and the metastases were controlled by roentgen ray. When she died, at the end of seven and one-half years, of a cardiac lesion there were still multiple cicatricial nodules present but she had remained entirely well and had lived a normal life during this time.

One must not fail to realize because of the capacity of thyroid malignancy to vary widely in type, to vary widely in its capacity for distant metastases and particularly to vary greatly in its degree of radiosensitivity, that it is in all cases of the first importance to know the type of malignant thyroid tumor one is dealing with. This will influence one as to how much surgery to apply and will distinctly influence one as to how much radiation to apply.

In hopeful tumors, it will be justifiable to employ radiation dosages which may seriously upset the patient's general condition and, likewise, one may justifiably employ dosages which will result in permanent skin changes.

It is not easy to set down upon paper in what cases to apply surgery in patients with cancer of the thyroid, and it is particularly difficult to set down how much to do when it is applied. In this experience with these malignant

lesions of the thyroid, we have dealt with almost every variety of problem. While we have learned a great deal about what to do surgically with these cases, we have learned even more about what not to do in these cases. I know of no group of cases where judgment and experience pay higher dividends than in the decisions in these cases to withhold surgery entirely, to undertake complete radical removals, and to stop and give up any ideas of radical removals after once undertaken.

In the patient with a discrete adenoma with an unruptured capsule, even though the tumor be of such firm consistency that malignancy is suspected, it is in our opinion unnecessary to do more than complete removal of the adenoma with its capsule intact. It is unnecessary and unwise in this situation to undertake complete thyroidectomy together with removal of the thyroid adenoma. If, however, the malignancy has eroded the fibrous capsule of the adenoma and involved the parenchyma of one lobe of the thyroid it is important in such cases that the entire lobe and isthmus with the contained malignancy be removed intact. Provided the carcinomatous adenoma has involved but one lobe, it is unnecessary to perform a total thyroidectomy and remove the unaffected lobe. If recurrence is to take place at this stage, it is most likely to be in the lymph nodes and is best controlled by irradiation.

If carcinoma has involved the entire gland an attempt may be made to remove it by removing the entire thyroid gland with its contained malignancy, if the involved gland appears movable. Attempts may be made to remove such glands even when they are quite fixed, provided there is not fixed and infiltrating carcinomatous tissue *extending below the clavicles and into the mediastinum*.

It is important in the surgery of cancer of the thyroid to realize that the trachea with its cartilaginous rings and the fibrous sheath which envelops it are quite resistant to carcinomatous infiltration. In late malignant lesions of the thyroid one will at times find the cartilaginous rings of the trachea softened, at times collapsed, and at times the tracheal wall actually invaded. In many cases, however, which seem so fixed to the trachea that malignant infiltration seems certain, operative investigation will demonstrate that the fixation is due to a cicatricial layer of condensed connective tissue between the back of the malignant thyroid and the trachea without infiltration and permitting clean and complete removal of the thyroid gland.

In occasional cases the carcinomatous process so remains within the thyroid gland itself that extension to trachea and muscles does not occur, permitting easy and complete ablation of the entire thyroid. Even when the malignancy so involves the thyroid that there is firm fixation to the trachea one may explore the gland for its possible removal.

With the exception of the patient with a relatively benign and early papillary cystadenoma in an unruptured adenoma, it is our opinion that malignancy of the thyroid should never be treated by surgery alone but in combination with irradiation. There are many patients with advanced malignant lesions of the thyroid in which no operation should be undertaken other than that

of obtaining a biopsy specimen to settle its type and so its amount of radiation. In most patients with carcinomata of the thyroid too advanced for

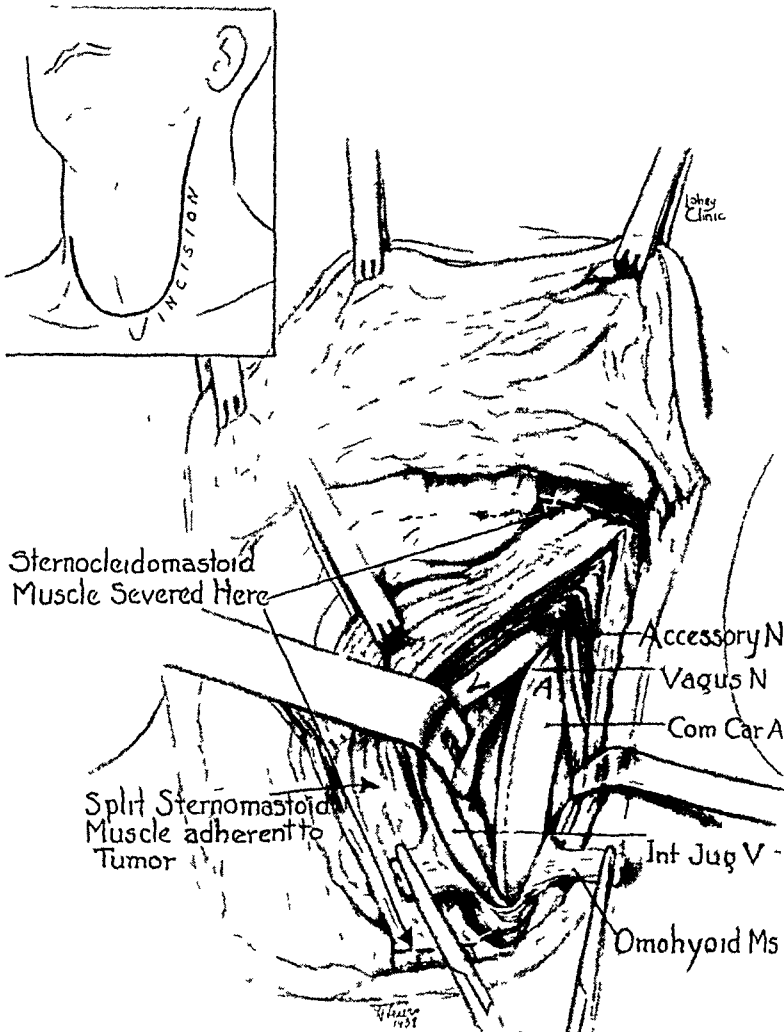


FIG 3—Note in the insert the type of incision with the limb on the side of the affected lobe carried well up to the angle of the jaw. This permits as shown in the main illustration wide exposure with high and low ligation of the internal jugular vein together with high and low transection of the sternomastoid muscle. It is possible with this exposure to remove the lobe involved by the malignancy with adjacent lymph nodes with most of the sternocleidomastoid muscle and all of the section of the internal jugular vein locally related to the thyroid malignancy. Since malignancy of the thyroid gland is so apt to extend along venous channels this is important as it removes unopened those venous channels connecting with the internal jugular the superior middle and inferior thyroid veins along which malignancy tends to spread. Note that a small strip of sternocleidomastoid muscle is left at the back that the internal jugular vein has been separated from the common carotid artery and the vagus nerve, thus establishing the cleavage line which is to represent the outer limit of the blocked out area to be removed. Note the dotted lines which mark the points above and below at which the sternomastoid muscle and internal jugular vein are to be severed establishing the upper limits of blocked out area for removal.

removal, there will be metastasis to the lymph nodes. The removal for biopsy of such a discrete and movable lymph node, often under local anesthesia, is a much easier and safer procedure than the exposure for biopsy of the infil-

CARCINOMA OF THE THYROID

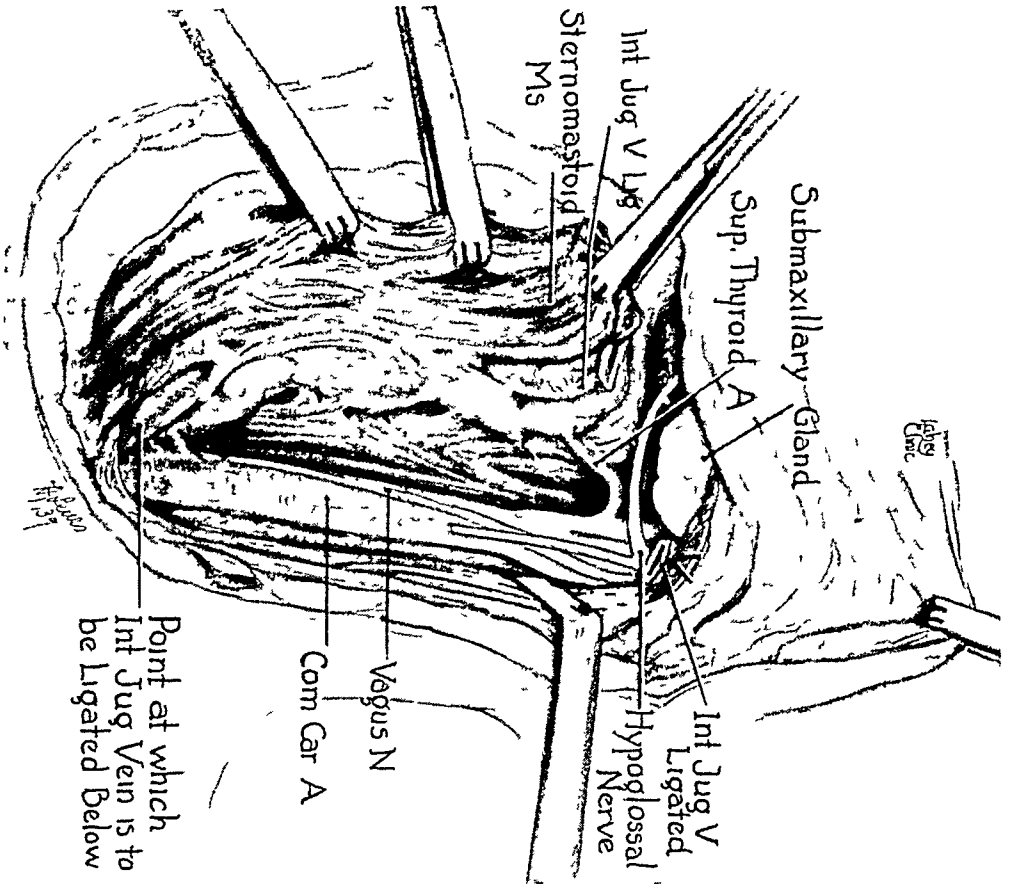


FIG. 4.—Illustrating the further development of the block removal of one lobe of the thyroid gland involved in malignancy, the sternocleidomastoid muscle and the entire neck segment of the internal jugular vein. In this illustration the upper segment of the sternomastoid muscle has been severed the internal jugular vein has been severed high between two ties and the upper portion of the block turned inward. The anatomic structures encountered are plainly shown and labeled so that they require no comment.

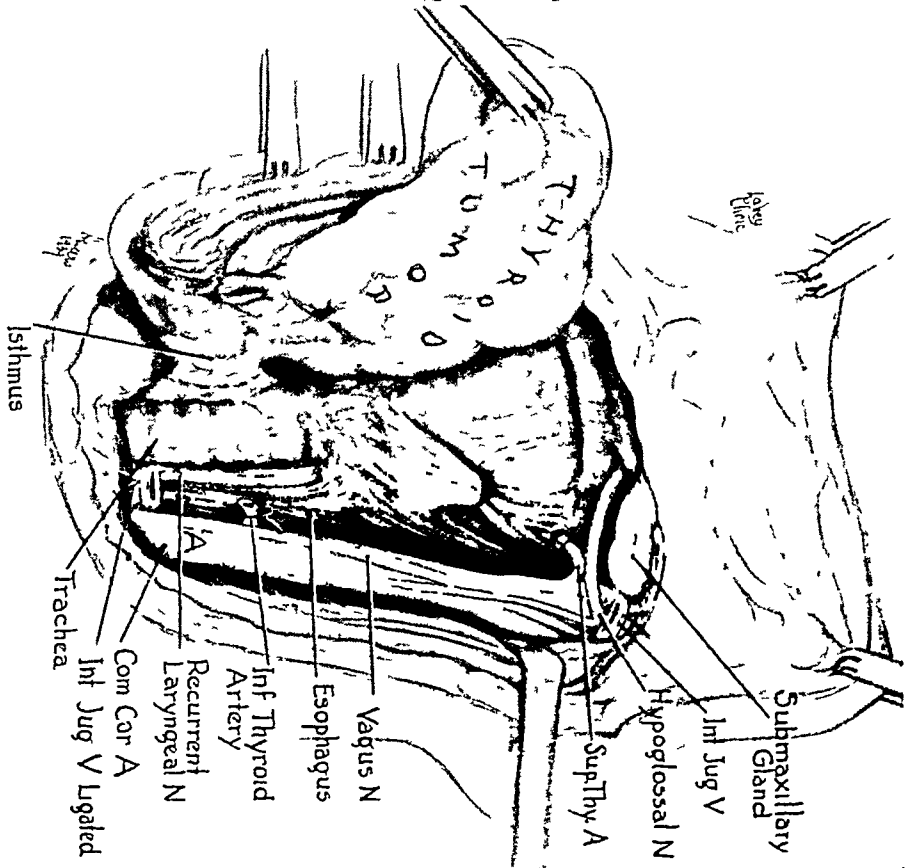


FIG. 5.—In this illustration the dissected block has been entirely freed and turned toward the median line so that it is attached to the remaining lobe of the thyroid gland by the thyroid isthmus which has been freed from the trachea. The sternomastoid muscle has been severed at its lowest point and the internal jugular vein has likewise been cut between ligatures at its lowest point in the neck. The recurrent laryngeal nerve is shown preserved as in the actual operative procedure. It was possible to separate and save the nerve without leaving behind obviously malignant tissue. It will frequently be possible to do this. Note that the descending branch of the hypoglossal nerve has been cut since the muscles which it supplies have been removed.

trated thyroid with the consequent bleeding and in a patient so obstructed in respiration that any anesthetic or manipulation on his neck may further add to his breathing difficulties

When malignancy of the thyroid has ruptured the capsule of the adenoma of the thyroid in which it started, when it has involved the surrounding thyroid parenchyma and when it has extended beyond the thyroid gland and involved the lateral and overlying muscles even with considerable fixation, provided the process is limited to one side of the neck, removal may still be attempted, not with any idea that it will accomplish complete surgical removal and a surgical cure, but to eliminate all of the tissue grossly involved in the malignancy. This gives irradiation less to accomplish and often so removes pressure from the trachea that complete relief of respiratory obstruction may be accomplished.

If radical surgical removal of an extensive unilateral carcinoma of the thyroid, in such a case as described above, with infiltration beyond the thyroid is attempted, the removal should really be radical and should proceed along definite lines. No attempt should be made to separate the muscles over the thyroid as in conventional thyroid operations. A high and wide skin flap should be turned up, leaving the platysma adherent to the front of the malignant gland (Fig 3). The internal jugular vein should be ligated just above the clavicle and just below the mastoid. The vein is severed at these points between the ties and the entire internal jugular separated from the common carotid artery and vagus nerve in the carotid sheath and left attached by its branches, superior, middle and inferior thyroid veins, to the malignant thyroid (Fig 4). If there be any extension into the muscles, the sternomastoid should be severed above and below and turned inward with the internal jugular vein and the malignant lobe of the thyroid. The superior and inferior thyroid arteries are tied and severed, and the entire lobe of the thyroid gland, with its contained malignancy, with the internal jugular vein attached to it and, if necessary, also with the sternomastoid muscle, is turned up and dissected inward until it is completely freed from the trachea and until the thyroid tissue in the remaining lobe is reached (Fig 5). In cases sufficiently extensive so that this radical procedure is justified, it is usually unwise to attempt dissection and preservation of the recurrent nerve although, even with quite extensive involvement of one lobe of the thyroid with malignancy, it will be found possible to dissect and preserve the nerve without limiting the radicalness and completeness of the removal of the carcinomatous lobe. One must realize in all operations for extensive thyroid malignancy that wide and complete removals of all tissue involved in the malignancy will not be possible.

The removal of the internal jugular, together with the malignant lobe of the thyroid, is of great importance in the surgical management of these cases due to the fact that thyroid malignancy so tends to extend into the veins and along their course. If the internal jugular be ligated and severed high and low in the neck then not only can the jugular itself be removed with the

malignant glands but also all the tributary veins, running from the thyroid into the section of the jugular which is removed, superior, middle and inferior thyroid veins can be removed. The tendency for recurrent thyroid malignancy to extend within the thyroid veins and the need for wide and radical removal of the adjacent veins together with the tumor in these cases, have been well stressed by Dr. Allen Graham. It is, likewise, important that this same principle be employed in the surgical management of recurrent thyroid malignancy.

In the surgical management of these malignant lesions of the thyroid, we have learned that it is unwise to continue attempting to remove malignant thyroids unless the dissections can be carried along definite anatomic lines of cleavage. If it is found that the malignant mass has, for example, grown into and fused with the trachea, it is better to give up any attempt at removing it than to attempt to cut away segments of its malignancy. It is particularly dangerous to attempt to remove masses of thyroid malignancy which have extended below the clavicles into the mediastinum. Extensions of thyroid malignancy from the lower poles into the mediastinum do so by infiltrating diffusely into mediastinal tissue and without establishing any definite lines of cleavage that permit safe separation and removal. Attempts to remove mediastinal extensions of thyroid malignancy result only in profuse venous hemorrhage with the postoperative occurrence of hematomata here that further embarrass respiration and permit the development of mediastinal infection. It is extremely important to appreciate that thyroid malignancy tends to extend backward in the neck into the groove between the trachea and the esophagus and that the esophagus is very prone to become attached to the malignant thyroid tissue often without actually being involved in it. As the malignant thyroid lobe is rolled inward for dissection, the malignant thyroid lobe often pulls up with it the attached esophagus. Many times we have had to carefully separate the pulled up and adherent esophagus from the malignant thyroid lobe before the lobe could be resected. Unless the thyroid malignancy has actually invaded the wall of the esophagus, that structure can readily be dissected away from the malignancy and permitted to fall back into its normal location. This is an extremely important point as the adherent esophagus can very easily be overlooked and injured. When adequate operations for malignancy of the thyroid have been completed, the trachea will be quite bare since all of the lateral lobe and isthmus will have been removed. There will, however, be instances in which, because of fusion of the growth with the trachea, it will not be possible to remove all of the tissue from over the trachea. In such cases, care must be taken to expose and clean off the trachea thoroughly, below the isthmus when it is possible, against the possibility that with postoperative swelling, edema and hematomata, the need for a tracheotomy may quickly and urgently arise. The time to prepare for a tracheotomy in any thyroid operation and particularly in thyroid operations for malignancy is when the first operation is being performed when there is good exposure, free breathing and when with a satisfactory unhurried dissec-

tion the trachea can be freed and exposed in a dry field. If when the operation for thyroid malignancy is completed there is the slightest question about the patient's breathing, the tracheotomy should be performed then and not later after the patient has suffered from hampered respiration and suboxygenation for some time. It will frequently be necessary to perform temporary tracheotomies in patients with extensive carcinomata of the thyroid who have had extensive dissections of the trachea.

TABLE II

PATHOLOGIC GROUPING OF MALIGNANT TUMORS OF THE THYROID*

Group I	Low or Potential Malignancy
	(1) Adenoma with blood vessel invasion
	(2) Papillary cystadenoma with blood vessel invasion
	(a) Originating from thyroid
	(b) Originating from aberrant thyroid
Group II	Moderate Malignancy
	(1) Papillary adenocarcinoma
	(2) Alveolar adenocarcinoma
	(3) Hurthle cell adenocarcinoma
Group III	High Malignancy
	(1) Small cell carcinoma (carcinoma simplex)
	(a) Compact type
	(b) Diffuse type
	(2) Giant cell carcinoma
	(3) Epidermoid carcinoma
	(4) Fibrosarcoma
	(5) Lymphoma

PATHOLOGY—The term "adenoma of the thyroid" has so frequently been misapplied to mere nodular aggregates of thyroid tissue that its present connotation is very indefinite. We regard as adenomata only those masses of thyroid tissue that can be considered definitely neoplastic. Certain of the tumors formerly regarded as adenomata would now be excluded and considered as foci of involutional change. For a true adenoma we require the following criteria to be fulfilled:

- (1) Complete encapsulation
- (2) Homogeneous texture, grossly and microscopically, throughout, with the exception of degenerative foci such as cysts, calcification, or fibrosis
- (3) Distinct variation of the tissue within the capsule from that outside
- (4) Evidence of compression of adjacent thyroid tissue by the nodules

We classify adenomata in four major groups, according to their histologic appearance. The embryonal adenoma is the least differentiated, made up of solid columns of small, compact, polyhedral, usually intensely basophilic cells, with varying amounts of a rather loose, edematous stroma. These resemble

* Modified from an earlier classification from this clinic.^{8, 9}

the structure of the thyroid gland in the earlier stages of embryonic life. The fetal adenoma is a somewhat more differentiated type, where there may be some small clusters of cells, but, in addition, there are some follicles containing a small amount of a rather thin, watery colloid. Again, the stroma is fairly abundant and edematous.

In the simple adenoma, the structure more nearly mimics that of the normal thyroid gland although it does not show the same degree of functional activity as does the adjacent normal thyroid tissue. Very rarely a true toxic adenoma may be discovered, in which there is hyperplasia and hyperfunction by the tissue of the adenoma itself and not as a result of the surrounding thyroid tissue. The bulk of the so-called toxic adenomata is composed of either nodules in an endemic goiter showing secondary hyperplasia or else true adenomata occurring in an hyperplastic gland. A subtype of adenoma, rarest of all, is the so-called Hurthle cell adenoma,¹² or as it is sometimes spoken of, the Getzowa adenoma. This is characterized by the presence of acini lined by large, pale, clear, acidophilic cells, with rather large, prominent, vesicular nuclei. These range from high cuboidal to columnar and are generally clearly demarcated from one another. Occasionally, they occur in masses or strands, but, in general, alveolar formation is fairly distinct.

The colloid adenoma is the most differentiated and one of the rare forms of tumor, where the acini are all greatly distended by huge aggregations of colloid. The epithelium is usually low cuboidal or flat. These may be occasionally mistaken for foci of hyperinvolution.

Any one of these types of adenomata may become malignant. Practically all have thin-walled blood vessels, and, as has been so clearly pointed out by Graham,¹³ one of the best evidences of malignancy in these tumors is the existence of blood vascular invasion.¹¹ Less than 3 per cent of adenomata show blood vessel invasion, and of those that show it, only 10 per cent show definite clinical evidence of malignancy. However, it is impossible to differentiate the small percentage of those adenomata with blood vessel invasion that do recur or metastasize from those that make no further trouble. Consequently, it is necessary to consider the whole group of adenomata with blood vessel invasion as potentially malignant, even though we recognize that 90 per cent will cause no further trouble. Undoubtedly, several factors are of importance here. The extent of the vascular invasion, the compactness of the growth, determining the ease with which emboli may form, and the site in which emboli may lodge.

The metastases of adenoma with blood vessel invasion vary in appearance, some are undifferentiated (Fig 6), others histologically indistinguishable from normal thyroid tissue. The commonest metastatic sites are the bones. The existence of bony metastases is not incompatible with long life, one patient seen having lived for seven years after a pathologic fracture called attention to the existence of the bony metastases. Those cases which show

gross evidence of blood vessel invasion are much more apt to show definite clinical evidence of malignancy than those with only microscopic evidence

It is important in determining the presence of blood vessel invasion to rule out artefact, whereby acini may seem to lodge within the lumina of vessels. We prefer to accept as definite evidence of blood vessel invasion only those cases in which actual penetration of the vessel wall may be made out. That such invasion must occur rather widely in these tumors is shown by the fact that the sections studied represent only a small fraction of the total mass of the tumor. So far, only one questionable case has been encountered where the usual routine examination of sections of the adenoma failed to disclose blood vessel invasion and subsequent development of metastases

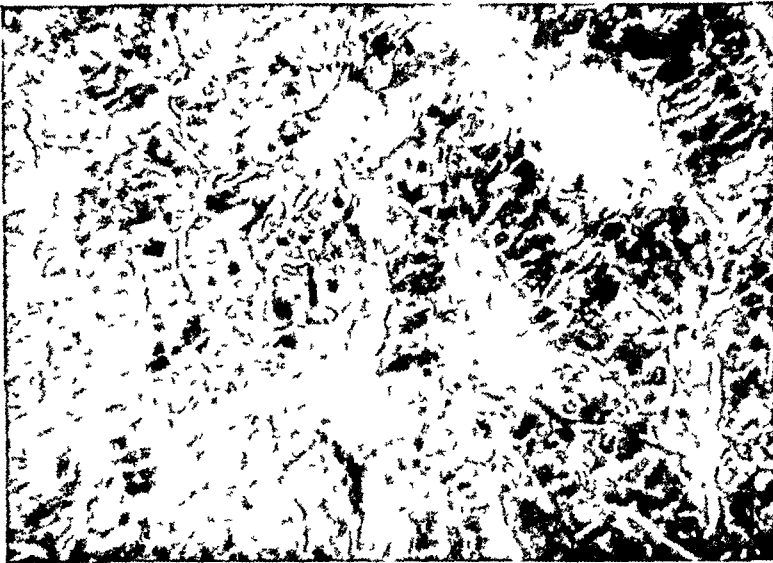


FIG 6—Embryonal adenoma of the thyroid showing undifferentiated cells and marked vascularity ($\times 300$)

proved the malignancy of the tumor, originally assumed to be benign, on the basis of the sections then taken

The great majority of the adenomata with blood vessel invasion are of the embryonal or fetal type. This type of invasion occurring in the simple, the colloid, and the Hurthle cell adenoma is practically unknown

In any discussion of the adenomata with blood vessel invasion, it is important to point out that this is not the only form of malignancy which may develop in an adenoma. In fact, almost any type of thyroid malignancy may appear on the basis of a preexisting adenoma, and, as has been known for years, 80 to 90 per cent of all thyroid tumors arise from preexisting adenomata. Therefore, there is sound pathologic and clinical evidence for the prophylactic removal of any isolated nodule of the thyroid gland which either is or simulates an adenoma

The malignant forms of papilliferous tumors of the thyroid and those of aberrant thyroid origin⁶ may be discussed together. There is but little essential difference in the behavior of the two groups. In reviewing the

older thyroid literature, it becomes obvious that regions of secondary hyperplasia with papillary projections in nodular goiters, as well as other changes, have been mistaken for true papilliferous tumors of thyroid origin.

First recognized by Wolf²⁵ who described both solid and cystic forms of papilliferous tumors, there was much confusion in the group until differentiated by Graham¹⁴. The peculiar clinical behavior of these tumors with their marked tendency to repeated local recurrences and failure to metastasize distantly was brought out clearly by Low¹⁷. Wegelin,²³ in his excellent discussion of the thyroid gland in Henke-Lubarsch, recognizes the existence of the solid and cystic form and recognizes also that papillary proliferations of the nonneoplastic type may occur in other enlargements of the thyroid.

Graham classified the malignant papilliferous tumors into the papilliferous



FIG 7—Papillary cystadenoma illustrating marked papillary formation and tendency to develop cysts. Note invasion of the perithyroid tissue (X50)

cystadenocarcinoma of local malignancy, the malignant adenoma with papilliferous differentiation, in which distant metastasis may occur, and a form of papilliferous adenocarcinoma arising independently from any preexisting adenoma.

The classification of the papilliferous tumors has been further clarified by Moritz and Bayless¹⁹ who distinguished five forms of papilliferous tumors: (1) The papilliferous cystadenoma, a benign tumor which represents hyperplasia of the lining epithelium of a cystic adenoma, (2) the papilliferous adenoma, which represents epithelial proliferation of an hyperplastic type within the follicles of a preexisting adenoma, and is nonmalignant, (3) the papilliferous carcinoid, which is differentiated by these authors, probably mistakenly called "papilliferous cystadenomata" by earlier writers, which represents focal papillary hyperplasia, nonencapsulated in a nonneoplastic thyroid

gland, (4) the papilliferous adenocarcinoma arising from malignant change in a papilliferous cystadenoma, which shows capsular invasion or metastasis to regional lymph nodes, and (5) the papilliferous malignant adenoma, which shows a papillary intra-acinar hyperplasia in an adenoma with malignant characteristics, *i.e.*, blood vessel invasion, capsular invasion, and sometimes metastasis to regional lymph nodes

We include in the present paper only the last two types, and we place the last type—the papilliferous malignant adenoma—in the same clinical group with the malignant adenomata with blood vessel invasion, rather than with the true malignant papilliferous adenocarcinomata. Because of this difference in clinical behavior from the true adenocarcinomata showing some tendency to papillary formation, we have preferred to utilize for this group the term papillary cystadenoma, malignant (Fig 7). Sometimes there is no extension beyond the primary tumor which shows gross or microscopic evidence of malignancy when explored, but at other times the malignancy is apparent because of either lymph node metastases or because of extensive proliferation with tracheal constriction.

The adenocarcinomata of the thyroid we regard as of moderate malignancy and place in our clinical Group II. These adenocarcinomata almost invariably arise from preexisting adenomata. They differ from adenomata in that they develop a less differentiated type of growth, with greater variation of cell size and shape, much greater mitotic activity, and a marked degree of invasiveness of surrounding tissue. Usually, the development of the adenocarcinoma has destroyed all trace of the preexisting adenoma and this original nidus can be recognized only from the history given by the patient.

We divide the adenocarcinomata into three histologic groups.

First, the papillary adenocarcinoma. This differs from the papillary cystadenoma by its greater anaplasia and by its lack of encapsulation. The papillary adenocarcinoma freely invades both the thyroid and adjacent normal tissue (Fig 8). The epithelium is variable in size and shape, but generally polyhedral or cuboidal, with fairly well-defined cell boundaries. The papillary projections are not covered with a single layer of epithelium as in the case of the papillary cystadenoma, but rather the epithelium is heaped up several cells in thickness, here and there masses of cells occur without any lumina whatever, mitotic figures are moderately frequent and some variation in cell size is prominent. However, definite lumina formed by the tumor may show the formation of colloid.

The second type of adenocarcinoma shows no papillary projections and is made up of masses and strands of epithelial cells, usually cuboidal to polyhedral, arranged in a stroma which may be either scant or fairly abundant. Here and there in the clusters definite acini form and these rarely contain colloid (Fig 9). Not infrequently the mitotic figures may be definitely abnormal, with multiple spindles and marked variation in chromosomal number.

The third type of adenocarcinoma is the rarest, the Hurthle cell adeno-

CARCINOMA OF THE THYROID

FIG 8

FIG 9

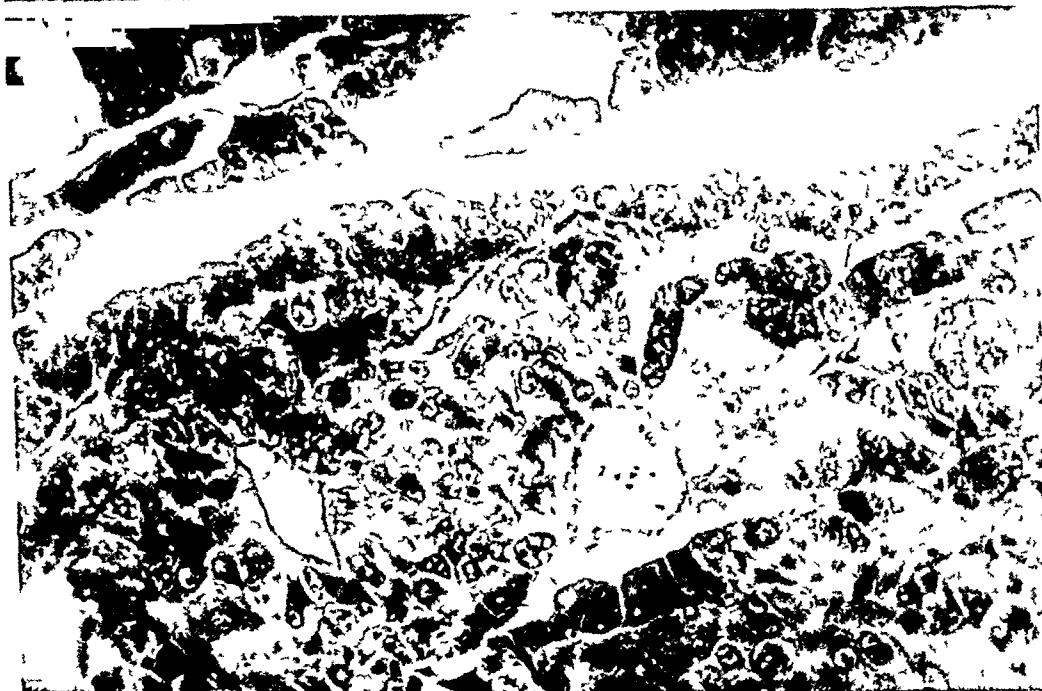


FIG 10

FIG 8—Papillary adenocarcinoma showing destruction of the thyroid and invasion of adjacent tissue (X48)

FIG 9—Adenocarcinoma showing polyhedral cells and slight tendency to alveolar arrangement (X300)

FIG 10—Hürthle cell adenocarcinoma with large, clear, acidophilic cells (X300)

carcinoma Here, the same large, clear, acidophilic cells predominate as are seen in the Hürthle cell adenoma, but their arrangement is irregular, small

FIG 11

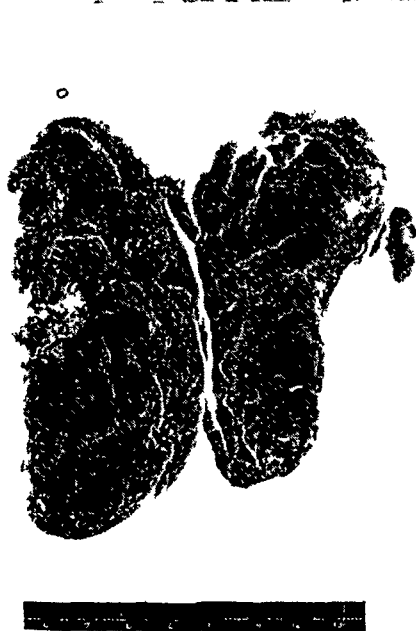
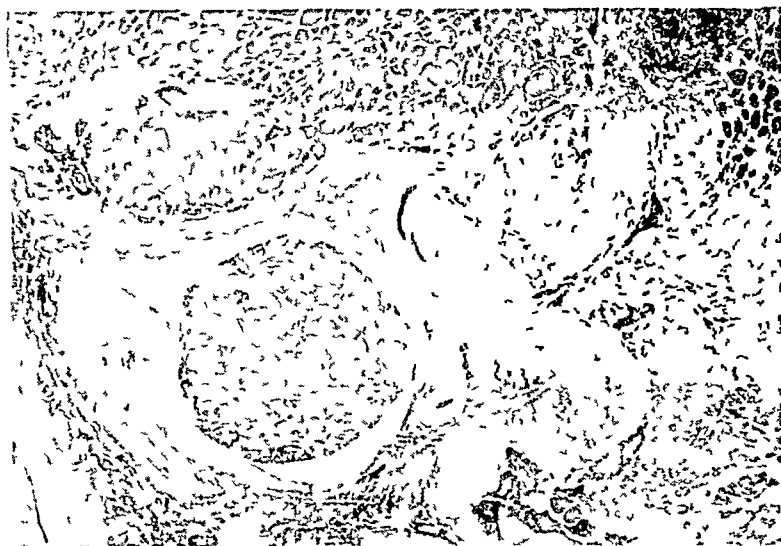


FIG 12



FIG 13

- FIG 11—Carcinoma simplex of compact type. Note the blood vessel invasion. ($\times 48$)
 FIG 12—Carcinoma simplex of the diffuse type showing resemblance to Hashimoto struma.
 FIG 13—Carcinoma simplex of the diffuse type demonstrating epithelial cells and irregular arrangement. ($\times 750$)

and large masses alternating with varying degrees of lumen formation (Fig 10). Usually colloid is not present. There is definite invasion of adjacent thyroid tissue and surrounding structures. Mitoses are moderate in number, usually only one or two per high power field. We believe this to be a true thyroid tumor, and not of parathyroid origin, as has been suggested

The highly malignant carcinomata of Group III represent a heterogeneous group from the histologic standpoint

The small cell carcinomata, or carcinoma simplex, occur in two forms in the thyroid. The first is the compact type, in which there are solid masses, strands and cords of rather small, cuboidal to polyhedral, deeply staining cells with hyperchromatic nuclei, with a sharply defined distinction between the tumor cells and their stroma (Fig 11). The mitotic figures are fairly frequent, ranging from one to five per high power field. Invasion of surrounding structures is marked.

In the diffuse form of carcinoma simplex of small cell type, we have a much more complicated picture. Here, at first glance, the tissue might be taken for chronic thyroiditis, particularly the Hashimoto type, at other times, the resemblance to lymphoma is marked (Fig 12). However, on careful examination, one sees that the cells of the tumor are made up of small, rather irregular epithelial cells with a very small amount of cytoplasm and a rather small hyperchromatic nucleus (Fig 13). Mitoses are rather infrequent. The tumor cells are scattered irregularly and diffusely through a rather dense, fibrous stroma, which has replaced much of the normal thyroid structure and extended out into the adjacent normal tissue. There are scattered lymphocytes and mononuclear leukocytes infiltrating the stroma as well. The clue to the true nature of the tumor is usually pointed out by small clusters of closely adjacent epithelial cells occasionally taking a pseudo-acinar form.

The giant cell carcinoma,²² sometimes called carcinosarcoma or even fibrosarcoma, has a very characteristic microscopic picture and a characteristic history. These tumors usually occur in females over 50 years of age, and show rapid growth arising from a previous long-standing adenoma. Grossly, they are fleshy, homogeneous, and widely infiltrating (Fig 14). Their appearance microscopically is bizarre in the extreme (Fig 15). All types of irregular tumor giant cells with huge, lobulated, often vacuolated nuclei, multiple nuclei, irregular mitoses are mixed indiscriminately with smaller clusters of fairly well-defined epithelial cells and some stromal fibroblasts. Few tumors have a more startling microscopic appearance than do these.

Epidermoid carcinoma of the thyroid is one of the rarest tumors. This has two possible sources of origin: thyroglossal duct remnants on the one hand, and metaplasia of thyroid epithelium on the other.¹⁶ In the instances we have seen, it has been practically impossible to tell from which source these tumors arise.

True fibrosarcoma may arise from the stroma of the thyroid gland, although it is extraordinarily rare.²⁶ The great majority of the cases of fibrosarcoma or of carcinosarcoma are the giant cell carcinomata which we do not regard as being of mesenchymal nature. The only criterion on which we are willing to accept the fibrosarcoma of the thyroid is that of a typical sarcoma arising within the substance of the thyroid, the cells of which show definite collagen or fibroglial fibrils (Fig 16).

True lymphoma of the thyroid may occur (Fig 17) and this must be distinguished from the carcinoma simplex of diffuse type. It must also be distinguished from the struma lymphomatosa of Hashimoto. The criteria for lymphoma here are the same as those elsewhere. Almost always, however, thyroid involvement is secondary to tumor elsewhere. The occurrence of definitely abnormal lymphoblastic cells arranged without regard to the anatomic conformation of the tissue infiltrated on the one hand and without

FIG 14

FIG 15

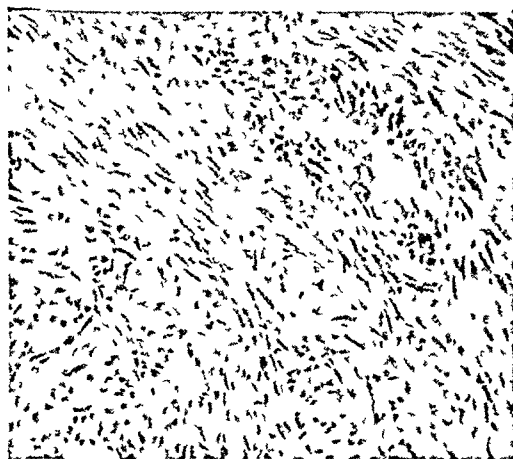
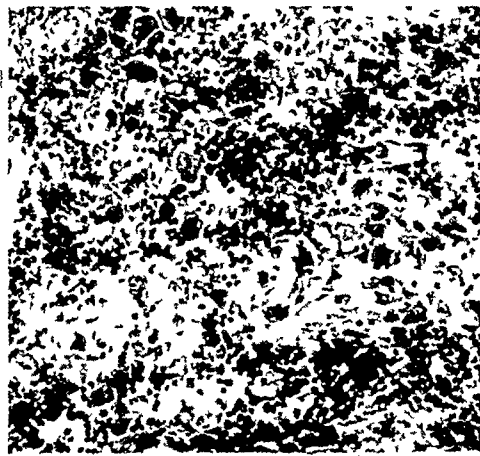
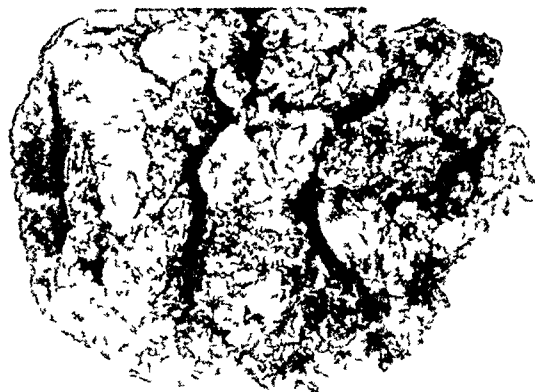


FIG 16

FIG 17

FIG 14—Giant cell carcinoma showing fleshy appearance and infiltrating character

FIG 15—Giant cell carcinoma note the large bizarre giant cells and irregularity of arrangement ($\times 300$)

FIG 16—Fibrosarcoma showing typical fibroblastic cells with abundant formation of collagen ($\times 250$)

FIG 17—Lymphoma of the thyroid. Cross section of the thyroid and trachea showing diffuse infiltration of tissues by lymphoma cells

regard to the formation of typical lymph nodular structures on the other hand is characteristic. While infiltration may be extensive in the struma lymphomatosa of Hashimoto, there is practically always clear-cut secondary follicle formation. The lymphocytes are normal in appearance and they infiltrate between the acini in orderly manner.

We have also seen Hodgkin's disease of the thyroid, which has exactly the same appearance and behavior as it has elsewhere

Radiation Treatment—The first report of the value of radiation therapy was by Pfahler,²¹ of Philadelphia, who reported a case in which operation was performed three times for carcinoma of the thyroid. The patient lived two years after beginning treatment and died of metastasis to the cervical spine. There was no evidence of local disease at the time of death. Pfahler reported another patient living and well three years following radiation therapy after partial excision and confirmation by histologic study.

In 1922, James Case⁷ reported a case of thyroid malignancy in which histologic evidence of malignancy was made at operation in 1914. Radiation treatment was started soon after surgical procedure and in 1922, eight years later, the patient was alive and well without evidence of recurrence.

Haagensen¹⁵ was the first to report the value of radiation therapy and to correlate it with the various histologic types, using the histologic classification suggested by Ewing.

Various studies have been made upon the frequency of malignancy in clinically nodular goiters. The incidence of malignancy, as reported by Balfour¹ in 1918, was 1.6 per cent in 6,359 cases of nonexophthalmic goiter at the Mayo Clinic. In J. H. Means¹⁸ monograph on the thyroid, he mentioned that carcinoma was proved to be present in 3.2 per cent of clinically nodular goiters.

In 1937, Murphy and Ahnquist²⁰ demonstrated that proliferation may take place in multiple colloid adenomatous goiters forming nodules and classed as tetral adenomata.

Radiation treatment of carcinoma of the thyroid has been employed since 1914 and varying reports in the literature give evidence of its value, although there are several instances of moderately large series of cases in which radiation therapy has been employed and no beneficial effects were obtained. It is to be noted that during the first years of treatment radiation was given merely as a palliative measure to control the disease symptomatically for as long as possible. During this time the pathologic classification was satisfactorily developed, as was the surgical treatment, and to-day we are in a position to judge the pathologic type of thyroid cancer which will respond to radiation therapy. It is not only with a palliative intent that we now start treatment but with the desire to bring about five- and even ten-year cures of this disease which heretofore has been practically impossible in the more severe types of thyroid malignancy.

It will be noted from the pathologic classification given in this paper that thyroid tumors must be divided into two types, namely, benign and malignant. We are not interested in the benign type since such tumors are handled satisfactorily surgically, and no radiation treatment is indicated. Radiation therapy for the benign types of thyroid tumor is contraindicated. It is on the malignant group that radiologists must center their attention and realize

there are several degrees of malignancy with which they must deal. We know that the tumors falling into Group I are of low or potential malignancy, and in many of the cases temporary if not permanent cure can be obtained by surgery alone. It has been our experience, however, in the advanced cases, in which radical operation cannot be performed, that many of these tumors decrease in size and some disappear following moderate amounts of radiation treatment, and in those cases in which recurrence took place after operation radiation therapy was of distinct value in controlling the disease over a period of years. It seems necessary to us in each case of thyroid cancer to give radiation therapy, even though the tumor is of low and potential malignancy. We believe the results reported in this paper will bear out the necessity of radiation treatment to obtain a high percentage of cures.

In the tumors of Group II and Group III, which are of moderate and high malignancy respectively, only a few will respond favorably to operation alone and we now know that most of the good results with radiation come when as much of the tumor has been removed surgically as possible. The end-results depend upon radiation therapy being given in large, protracted doses to destroy the tumor completely. Our experience with some types of tumor in the high malignancy group has been small, namely, the giant cell carcinoma and the epidermoid carcinoma. It has been impossible to determine the lethal tumor dose of radiation necessary to destroy these tumors, but in no case has a satisfactory result been obtained even when radiation was used as a palliative procedure. We believe from the few cases of this type which we have seen that it will be impossible to destroy giant cell or epidermoid carcinoma without destroying normal surrounding tissue.

In the moderately malignant group, namely, the papillary adenocarcinoma, the alveolar adenocarcinoma, and the Huthle cell carcinoma, it is of interest to note that prior to 1932 operation plus radiation treatment was of practically no value except in isolated cases. The results in this group of cases show that the improvement is now brought about by the larger doses of roentgen rays given postoperatively.

We start radiation treatment as soon after the surgical operation as the condition of the patient warrants, which is usually within one week. There need be no fear of the wound failing to heal by giving radiation therapy after five days. A large percentage of the patients here reported have been treated by a routine method in order to determine the lethal tumor dose of the various types of malignant cells. We have learned the amount of radiation necessary to destroy those tumors which can be successfully treated by radiation.

A cross-fire method of radiation has been found to be preferable in this type of lesion. One treatment is given daily to each of three portals, using one portal on each side of the neck and one in the midline, being careful not to overlap the fields but centering the rays so that the largest percentage of the radiation will enter the tumor bed. The size of the portal depends on the size of the original growth and the degree of substernal extension which the tumor has attained. We have usually been able to use a 7 cm square

portal on each side of the neck and in the midline without overlapping the field, and in this way have covered the entire tumor bed. A total of 2,000 r units is given to each portal, to make a total dose of 6,000 r units delivered to the skin during one series of treatments. Each portal is treated daily after the first three treatments, giving 150 r units to each, making a total of 450 r units daily. If the patient is debilitated it is necessary to decrease the dose to 100 r units to each portal daily. A total of 6,000 r units given externally on the surface gives a dose of approximately 4,800 r units 2 cm beneath the skin area, which we believe is fair to assume as the total depth dosage, although no direct measurements have been made in our cases. The following factors have been used:

K V P 200, milliamperes 20, r units per minute 24

Filter 1 Mm copper, 1 Mm of aluminum added

Distance 50 cm, portal 7 sq cm, half value layer 0.11

Treatments are carried on daily except Sunday unless complications arise

Complications of Radiation Treatment—The most common complication of radiation treatment is radiation sickness which is quite common when large amounts are administered. Radiation sickness may come on immediately following the treatment or two to six hours later. The symptoms are nausea and vomiting, associated with a generalized feeling of unrest and irritability. We have tried numerous medications to control radiation sickness but for the most part none of them has been successful, although in a few cases striking results have been obtained by the use of vitamin B₁ in large doses. This is not a serious complication as it usually clears within 72 hours after radiation has been completed.

The most important complication following radiation treatment is radiation dermatitis which may in some cases be quite severe and require six to eight weeks to heal entirely. Radiation dermatitis will occur with this dosage in approximately seven to ten days following treatment. Laryngitis and tracheitis as well may develop but disappear in nine to ten weeks' time.

We have had no fatal results from radiation treatment alone, but several of our patients have had to be hospitalized owing to difficulty in swallowing following treatment.

Results—In tabulating the results of this series of cases it was necessary to review the entire group of cases of thyroid cancers which have been studied in the clinic from a clinical and pathologic angle in order to reclassify these tumors properly. In so doing, all questionable cases of malignancy were discarded and the tabulation of our results varies from that previously reported. We believe by so studying these cases we have been able to correlate successfully the clinical, pathologic and radiologic pictures of this disease.

SUMMARY

The relationship of malignancy to preexisting adenomata of the thyroid gland is discussed.

Illustrative cases demonstrating the penalty of delay in the removal of discrete adenomata are presented

The clinical diagnosis of malignancy of the thyroid is discussed, together with the diagnosis, management, and dangers of malignant degeneration in lateral aberrant thyroid

The surgical approach to malignancy of the thyroid gland combined with roentgenotherapy is discussed and the method of radically removing one or both lobes of the thyroid, with the sternomastoid muscle and internal jugular vein is discussed and illustrated

Mention is made of the contraindications for undertaking operation and the contraindications for continuing operation after it has once been undertaken

The pathology of thyroid malignancy, together with a grouping, is presented

The radiation treatment of thyroid malignancy and the five-year survival rates following combined radiation and surgical treatment are presented

BIBLIOGRAPHY

- ¹ Balfour, D C Cancer of the Thyroid Gland *Med Rec*, 94, 846, November 16, 1918
- ² Billroth, Theodor Uber eine seltene Geschwulst am Halse—Eine Jodschiemerkur Electropunctur *Deutsche Klinik*, 7 175-180, 1855
- ³ Bloodgood, J C Cysts of the Thyroid Gland *Surg, Gynec, and Obstet*, 1, 113-137, August, 1905
- ⁴ Burns, Allan Observations on the Surgical Anatomy of the Head and Neck Glasgow, Wardlaw and Cunningham, 1811, pp 207-225
- ⁵ Case, J T Discussion of Symposium on Therapy of the Thyroid Gland *Am Jour Roentgenol*, 9, 30, January, 1922
- ⁶ Cattell, R B Aberrant Thyroid *J A M A*, 97, 1761-1767, December 12, 1931
- ⁷ Chetwinds, M J *Handb d Chir Heidelberg*, 1822-23
- ⁸ Clute, H M and Smith, L W Cancer of the Thyroid Gland *Arch Surg*, 18, 1-20, January, 1929
- ⁹ Clute, H M, and Warren, Shields Cancer of the Thyroid Gland *Am Jour Cancer*, 15, 2563-2582, October, 1931
- ¹⁰ Cohnheim, J Einfacher Gallertkropf mit metastasen *Virchows Arch f path Anat u Physiol*, 68, 547-554, 1876
- ¹¹ Ehrhardt O Zur Anatomie u Klinik der Struma maligna *Beitrag z klin Chir*, 33, 343, 1902
- ¹² Eisenberg A A, and Wallerstein, H Hurthle Cell Tumor *Arch Path* 13, 716-724 May, 1932
- ¹³ Graham, Allen Malignant Epithelial Tumors of the Thyroid *Surg, Gynec, and Obstet*, 39, 781-790, December, 1924
- ¹⁴ Graham, Allen Malignant Tumors of the Thyroid—Epithelial Types *ANNALS OF SURGERY*, 82, 30-44, July, 1925
- ¹⁵ Haagensen, C D Carcinoma of the Thyroid Its Radiosensitivity *Am Jour Cancer*, 15, 2063-2105, July, 1931
- ¹⁶ Jaffe, R H Epithelial Metaplasia of the Thyroid Gland, with Special Reference to the Histogenesis of Squamous Cell Carcinoma of the Thyroid Gland (Abstract) *Am Jour Path*, 13, 671, July, 1937
- ¹⁷ Low, H C Papillary Adenocystoma of the Thyroid and Accessory Thyroid Glands *Boston Med and Surg Jour*, 149, 616-623, December 3, 1903

- ¹⁸ Means, J H The Thyroid and Its Diseases Philadelphia, 1937, pp 602
- ¹⁹ Moritz, A R, and Bayless, F Papilliferous Tumors of Thyroid Gland and of Aberrant Thyroid Tissue Am Jour Path, 7, 675-689, November, 1931
- ²⁰ Murphy, W B, and Ahnquist, G Origin of Fetal Adenoma in Thyroid Gland Arch Surg, 35, 211-233, August, 1937
- ²¹ Pfahler, G E The Treatment of Malignant Disease by Means of Deep Roentgenotherapy and Electiothermic Coagulation Surg, Gynec, and Obstet, 24, 14-29, January, 1917
- ²² Smith, L W Certain So-called Sarcomas of Thyroid Arch Path, 10, 524-530, October, 1930
- ²³ Wegelin, C Schilddruse, in Henke F and Lubarsch, O Handbuch der speziellen pathologischen Anatomie und Histologie Berlin, Julius Springer, 1926, 8, 20
- ²⁴ Wilson, L B Malignant Tumors of the Thyroid ANNALS OF SURGERY, 74, 129-184, August, 1921
- ²⁵ Wolfler, Anton Über die Entwicklung und den Bau des Kropfes Arch f klin Chir, 29, 1-97, 754-866, 1883
- ²⁶ Zeckwer I T Fibrosarcoma of Thyroid Arch Surg, 12, 561-570, February, 1926

STUDIES RELATING TO THE PATHOGENESIS OF CHOLECYSTITIS, CHOLELITHIASIS AND ACUTE PANCREATITIS *

J DEWEY BISGARD, M D , AND CHARLES P BAKER, M D

OMAHA, NEB

FROM THE DEPARTMENTS OF SURGERY, PHYSIOLOGY AND PATHOLOGY, UNIVERSITY OF NEBRASKA
COLLEGE OF MEDICINE OMAHA NEB

UNTIL comparatively recently the pathogenesis of both cholecystitis and cholelithiasis was ascribed solely to infection. Since, however, there were several clinical and pathologic features about the disease which were inconsistent with this hypothesis, investigation was stimulated. From the studies there have accumulated many excellent clinical and experimental data which not only minimize further the importance of infection but establish, rather definitely, certain other pathogenic factors.

There has accumulated a preponderance of evidence to indicate that biliary stasis is a very constant and, therefore, basic factor, but there is also good evidence that stagnation of bile does not in itself cause permanent pathologic changes in the gallbladder. Such changes are, in all likelihood, dependent upon other agents which either accompany stasis or result indirectly from it.

It has been demonstrated repeatedly that the wall of the gallbladder becomes edematous or inflamed from several factors, among which may be mentioned abnormal changes in the chemistry of the bile, particularly as these relate to alterations in its hydrogen ion concentration, the presence of pancreatic enzymes in the bile, and overdistention of the viscus. It has also been demonstrated repeatedly that when the gallbladder wall is edematous or inflamed its selectivity in its absorptive and secretory capacity becomes altered. Likewise, the damaged wall becomes more vulnerable to infection. Thus, an abnormality in the constituency of bile due to stasis, hepatic damage, the presence of pancreatic ferments or other factors, may cause pathologic changes in the wall of the gallbladder and, in turn, these changes alter further the chemistry of the contained bile and upset the balance by which certain of its constituents are held in solution. This results in their precipitation and the formation of stones. For example, it has been shown that when the bile salt-cholesterol ratio falls below a critical level, cholesterol crystals appear in the bile.

Detailed accounts of these facts and other related clinical and experimental observations are recorded in the reports of the excellent studies of Rous, McMaster and Drury, Ivy and Walsh, Mann, Foster and Brimhall, Andrews, Schoenheimer, Hidina, Dostal and Aronsohn, Elman and Graham, Plemister, Aronsohn, Pepinsky, Day and Hastings, Ravdin, Johnston, Austin, Riegel and Rose, Dolkart, Jones, and Brown, Doubilet and Colp, Cooper and Illingworth, Whitaker, Feldman, Morrison, Krantz and Carr, Walters, Greene and Fredrickson, and Wolfer.

* Read before the American Surgical Association, St. Louis, May 1, 2, 3, 1940

In an excellent piece of work, Wolfer has presented evidence which suggests that, under certain circumstances, pancreatic juice in man could and unquestionably does pass by reflux into the gallbladder. He, among others, quoted by him, has shown that the instillation of unfiltered pancreatic juice into the gallbladder of animals is followed by pathologic changes which vary from edema to complete necrosis of the wall. The same results were produced by instillations into the common duct. This subject of pancreatic reflux has



FIG 1.—Postoperative cholangiogram. Iodized oil injected through a catheter in the common duct filled not only the much dilated biliary ducts but also the duct of Wirsung. There is a filling defect at the ampulla of Vater presumably from a stone impacted in it. None of the radiopaque solution entered the duodenum. The common passage way between the common duct and the duct of Wirsung is well demonstrated in addition to the obstruction and stasis and dilatation of the ducts resulting from it (Courtesy of Dr R. R. Best)

been discussed at length by Wolfer so only a few salient facts will be presented here. It is a pertinent fact that the pancreatic duct joins the common duct or shares with it a common opening at the ampulla of Vater in a large percentage of people. Mann and Giordano found this relationship in 45 per cent of the specimens which they studied, while Cameron and Noble, Westphal, and Elman found it to exist in 65, 84 and 59 per cent, respectively. With an obstruction at the ampulla, as shown in Figure 1, this continuous passageway between the ducts permits pancreatic secretions to mix with the

bile in the common duct and with it pass into the gallbladder. Reflux of this sort unquestionably takes place in the presence of obstruction and therefore in conjunction with stasis. It is possible that it occurs in the absence of obstruction and stasis. That pancreatic secretions do enter the gallbladder in man has been shown repeatedly by demonstrating the presence of pancreatic enzymes in the gallbladder bile in cases with acute cholecystitis.

Our interest in the subject of pancreatic reflux was aroused by observations made upon a patient who died from total loss of bile and pancreatic secretions through a cholecystocutaneous sinus.

Case Report—A male, age 38, had, when seen by his surgeon, a typical clinical picture of acute cholecystitis of 12 hours' duration. There had been two previous similar attacks of pain within the past three months. A mild degree of jaundice which had followed the second episode had persisted up to the onset of the present one.

He was operated upon immediately, and a moderately distended, thick-walled, markedly edematous and inflamed gallbladder was found amid a few fibrinous adhesions and a small amount of bile stained fluid. The gallbladder contained no stones. A cholecystostomy was performed.

Immediately following operation and continuing until his death 12 days later, there was a very copious and almost continuous drainage of clear or slightly bile tinged fluid. It drained through the tube for 48 hours and thereafter from the wound.

He was seen in consultation by one of us (J. D. B.) on the sixth day after operation. The wound in the abdominal wall was wide open and its surfaces fiery red. Copious quantities of clear fluid welled up in the wound almost constantly. The skin of the abdominal wall for a wide area about the wound was fiery red and showed considerable digestion.

The patient was extremely dehydrated despite the parenteral administration of two to four liters of fluids daily. The eyes and cheeks were sunken, the pulse thin, its rate 120 to 140, the blood pressure 80/40, the rectal temperature 96.2° to 98° F., and there was extreme asthenia. Blood chlorides were 210, sodium 205, and potassium 25.

With restoration of a more nearly normal fluid and mineral balance by increasing intake, the temperature, pulse, blood pressure, and urinary output assumed fairly normal levels and the general appearance improved remarkably for a few days.

From a first impression a diagnosis of duodenal fistula (probably originating from a surgical accident) was entertained. However, aniline dyes and charcoal, given by mouth, did not appear in the fluid draining from the wound and could not be demonstrated in it. But the dyes subsequently appeared in the stools. Lipiodol, injected through a catheter which had been passed for some distance into the sinus tract, filled the extrahepatic ducts down to the ampulla where a small quantity entered the pancreatic duct. None entered the duodenum.

The drainage fluid contained both amylase and trypsin in the two samples examined. A postmortem examination could not be obtained. However, from the evidence, there can be little doubt that there existed a complete obstruction at the ampulla, and, as a result pancreatic secretions passed up the common and cystic ducts and through the gallbladder to be discharged through the sinus.

We have subsequently operated upon two cases with acute nonperforated gangrenous cholecystitis with regional bile peritonitis. Cultures from the abdominal fluid, from the bile, and from the wall of the gallbladder in both cases were sterile. But the gallbladder bile in both cases contained both amylase and trypsin. The peritoneal fluid was not examined for enzymes. Colp, Geibel, and Doubilet have reported three similar cases. Two had bile

peritonitis and sterile gallbladder bile. In one, the bile contained *B. coli* and *B. Friedlander*. In all of them, the gallbladder bile contained pancreatic enzymes.

Many of the current opinions regarding the pathogenesis of gallbladder disease are based upon observations made upon laboratory animals which seldom, if ever, develop the disease. There are, however, certain domestic animals—cattle, sheep and goats—which frequently develop gallbladder disease. Yet the problem as it exists in these animals has received little or no attention. Nor have these animals been utilized for purposes of investigating the problems of gallbladder disease. With these thoughts in mind, several visits were made to a local packing house and some interesting facts were

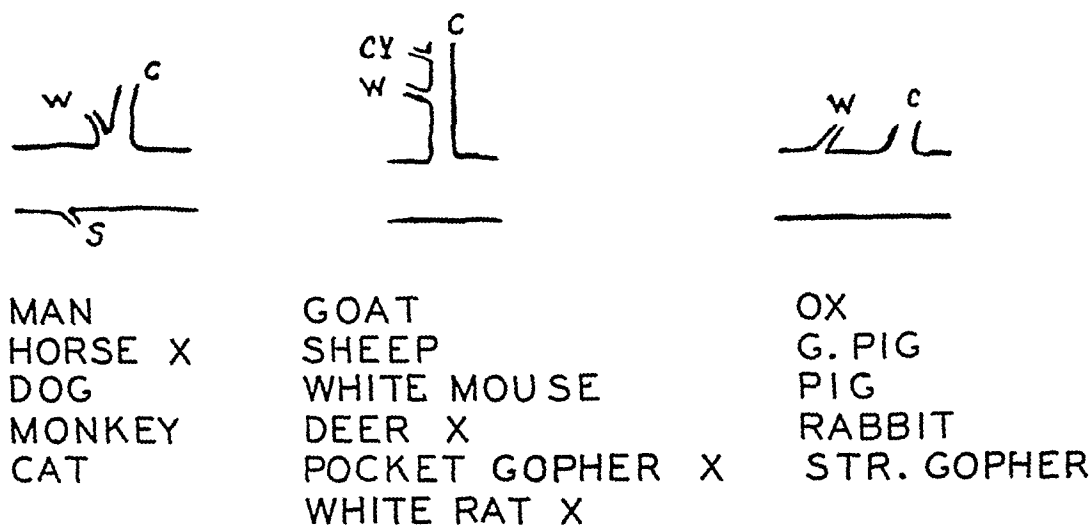


FIG. 2.—Diagrammatic illustration of the anatomic arrangement of the common hepatic and pancreatic ducts in man and in the common laboratory and domestic animals (taken from Mann, Foster and Brimhall). (X) Animals which have no gallbladder. Ducts (C) Common hepatic, (CY) Cystic, (W) Wirsung, (S) Santorini.

obtained. Gallbladder disease occurs infrequently in swine, commonly in sheep and goats, and less commonly in cattle. It occurs principally in the form of stones, and almost entirely in the older animals. The stones, with few exceptions, are of one type, i. e., bile pigment. In most instances, the gallbladder containing the stones is normal in gross appearance.

In sheep, however, chronic cholecystitis, with or without stones, occurs not infrequently, and curiously enough the liver and bile ducts of animals in which there is cholecystitis usually show evidence of active or past infestation with liver flukes. Since these parasites are large, it would appear that they might readily produce a temporary obstruction of the common bile duct as they ascend it. This possibility should be borne in mind in connection with the anatomic arrangement of the ducts as shown in Figure 2, and the experimental observations which follow.

EXPERIMENTAL STUDIES

As stated above, all previous investigations of gallbladder disease have been carried out in animals which, under normal circumstances rarely, if ever, develop the disease. Furthermore, the experimental procedures which

have been employed to study various phases of the problem have had to introduce, as a matter of necessity, certain unphysiologic and undesirable factors

Goats were used in our experiments because the reaction of their gallbladder bile differs little from that of human, because they normally develop gallstones and cholecystitis with a fair degree of frequency, and because the anatomic arrangement of their duct system is remarkably well adapted to the purposes of this study

In a search for information regarding comparative mammalian anatomy of the hepatic duct system, the report of the observations of Mann, Foster and Bimhall was found. These observations are illustrated in Figure 2. It

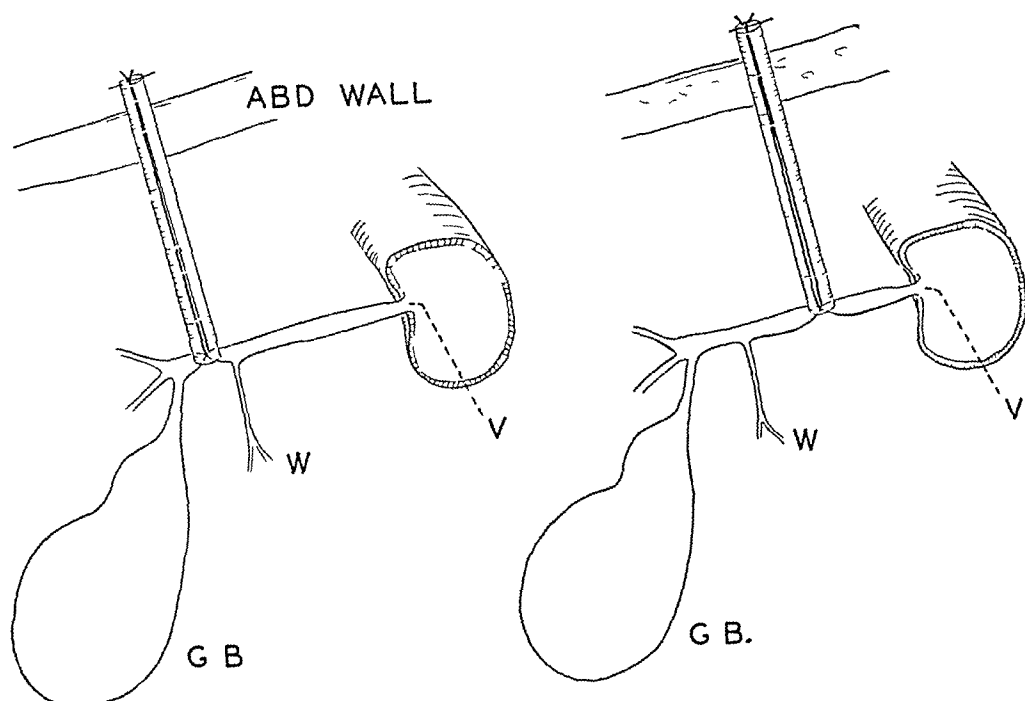


FIG 3—Diagrammatic illustration showing the method of inducing temporary obstruction of the common duct. The duct was encircled with a loop of dermal suture which was threaded through a glass tube with the ends of the loop tied over a button which capped the exteriorized end of the tube. The obstructions were released by cutting the exposed ends of the loop and removing it with the tube. Obstructions above the duct of Wirsung (W) induced stasis only, below it, stasis plus the reflux of pancreatic secretions. (V) Ampulla of Vater. (G B) Gallbladder.

will be observed that in both goats and sheep the pancreatic duct empties into the common bile duct at a considerable distance proximal to the juncture of the common duct with the duodenum and several millimeters distal to the juncture of the common and cystic ducts. Thus, normally, pancreatic juice mixes with bile in the proximal end of the common duct. It occurred to us that in the event of an obstruction at the distal end of the common duct, not only would stasis be produced but also an opportunity would be afforded for the reflux of pancreatic secretions into the gallbladder and of bile into the pancreas. On the other hand, an obstruction of the common duct immediately proximal to the pancreatic duct and yet distal to the cystic duct would result in biliary stasis alone. If we assume that stasis and reflux in man are brought about by an obstruction at the ampulla of Vater, then we have, in man, a

situation closely simulating that produced in our experiments, by the simple expedient of temporarily or permanently occluding the ducts. By obstructing the common duct at the two levels (above and below the pancreatic duct) an opportunity was afforded for a comparison of the effect upon the gallbladder of stasis alone with that of stasis plus the reflux of pancreatic secretions.

The common duct was obstructed by two methods. In one group of goats, the obstructions were made permanent with ligatures of silk. In the other group, temporary obstructions were created by means of plain catgut ligatures in two goats and by a special method in the remaining ones. This method consisted of passing a loop of dermal suture material around the common duct. The ends of the loop were threaded through a glass tube and tied over a button which capped the outer end of the tube. This tube was long enough to extend from the common duct out of the abdomen and beyond the surface of the skin. Obstructions were maintained for periods varying from 24 hours to six days. They were released by cutting the exteriorized ends of the loop and removing it with the tube (Fig. 3).

PROTOCOLS OF EXPERIMENTS

Classified Report of Individual Animals

GROUP 1—*Permanent Obstruction Distal to Junction of Pancreatic Duct*

Goat No. 4—Approx. age, one month. *Diagnosis*: Acute nonperforated gangrenous cholecystitis with bile peritonitis and acute pancreatitis with local fat necroses.

The common duct was obstructed by permanent ligature distal to the entrance of the pancreatic duct. The animal was killed when moribund, three days later.

Gross Pathology—Tissues of the abdominal wall and peritoneal cavity were bile stained. The abdomen contained several ounces of bile stained fluid, but there were no adhesions. The gallbladder was enormously distended but intact and its surface was dull and deeply stained. It contained thick dark brown fluid, turbid with chunks of reddish brown and black friable material. The fluids from the peritoneal cavity and gallbladder were sterile on culture, and both contained amylase (activity of 20 and 100, respectively). The gallbladder fluid also contained trypsin (activity of 1.2) and occult blood. The extrahepatic ducts were moderately dilated above the ligature. The pancreas was enlarged, tense, and studded with reddish brown areas, and the surrounding tissues showed fat necrosis. Proximal to the ligature all extrahepatic ducts were greatly dilated. The liver was pale, enlarged and its edges rounded. The regional lymph nodes were enlarged.

Microscopic Findings—Gallbladder: The epithelium was gone except for minute scattered remnants in the depths, and there was edema of all layers but principally of the serosa and all tissues were partially necrotic. There was no cellular infiltration. Pancreas: The ducts were dilated and many contained bile. Throughout there were areas of fat necrosis and digestion of the acinar tissue. Liver: There was much bile pigment and some congestion. Kidneys: Normal.

Goat No. 5—Approx. age, one month. *Diagnosis*: Acute cholecystitis, early acute pancreatitis and early multiple liver abscesses. Pneumonia.

The common duct was obstructed by permanent ligature distal to the entrance of the pancreatic duct. Death occurred 22 hours later. There was bronchopneumonia of both lungs.

Gross Pathology—The gallbladder was free from adhesions and moderately distended, and the extrahepatic ducts were moderately dilated above the ligature. The gallbladder fluid was thick, brown, and contained reddish brown soft masses. Cultures of the fluid were negative. Pancreas was enlarged and tense, and on its surface were scattered red areas. The liver was enlarged and slightly mottled. There was regional lymphadenopathy.

Microscopic Findings—Gallbladder: The surface was devoid of epithelium except in the depths of the folds. There was moderate edema of the wall, mainly of the serosa and some pigment in the submucosa, but nowhere any cellular infiltration. Common duct: Changes were essentially the same as those of the gallbladder except that the tissues were partially necrotic. Pancreas: Scattered areas of digestion and necrosis but no infiltration of leukocytes. Liver: A few areas of necrosis with and without collections of polymorphonuclear cells. Kidneys: Normal.

Goat No. 7—Approx. age, one month. *Diagnosis*: Acute nonperforated gangrenous cholecystitis with bile peritonitis, early acute pancreatitis and multiple early liver abscesses.

The common duct was ligated distal to the entrance of the pancreatic duct. Death occurred 20 hours later.

Gross Pathology—The upper part of the abdomen contained a few ounces of a bile stained fibroseropurulent exudate. The gallbladder and ducts were moderately distended but intact. The gallbladder fluid was thin and turbid with bits of soft dark brown and reddish brown material. It contained occult blood and both trypsin (activity of 2.2) and amylase (activity of 80). Culture from the gallbladder wall and from the fluid were *B. coli* and gram negative cocci. The pancreas was enlarged, tense, firm, and mottled with reddish brown areas. The liver was enlarged and mottled.

Microscopic Findings—Gallbladder. Devoid of epithelium and the wall infiltrated extensively with lymphocytes and polymorphonuclear leukocytes. All tissues were undergoing necrosis. Common duct. Same changes as found in the gallbladder. Pancreas. Marked dilatation of both ducts and acini. There was necrosis of both fat and acinar tissue and infiltration with both lymphocytes and polymorphonuclear leukocytes. Liver. There were scattered areas of necrosis of liver cells with collections of both mononuclear and polymorphonuclear leukocytes.

Goat No. 8—Approx. age one month. **Diagnosis** Acute gangrenous nonperforated cholecystitis and acute pancreatitis with local peritonitis. Acute hepatitis with multiple abscesses. The common duct was permanently ligated distal to the juncture of the pancreatic duct. Autopsy five days later.

Gross Pathology—The tissues of the abdominal wall and peritoneal cavity were bile stained. There were two or three ounces of bile stained fluid in the right upper quadrant. The gallbladder was buried in a mass of adhesions and it and the extrahepatic ducts above the ligature were greatly distended. The gallbladder was slightly thicker than normal, dark green in color and had no tissue luster. It contained thin greenish brown fluid in which there were many particles of soft brown material. The fluid contained both trypsin (activity of 1.2) and amylase (activity of 100) and from the fluid were cultured *B. coli* and gram positive and negative cocci. The pancreas was enlarged, tense and bluish pink in color. Its duct appeared to contain bile. The liver was very large and mottled and its edges were round. Regional lymph nodes were much enlarged.

Microscopic Findings—Gallbladder. The epithelium was gone and the other tissues were entirely necrotic. The wall was considerably thickened by edema. Liver. There were small scattered areas in which hepatic cells were undergoing necrosis also multiple small abscesses characterized by collections of polymorphonuclear leukocytes. There was also an increase in young connective tissue. Pancreas. The pancreatic ducts were dilated and there were scattered areas of necrosis of acinar cells and of fat. All blood vessels were congested. Kidneys. Normal.

Goat No. 13—Approx. age one month. **Diagnosis** Acute cholecystitis. Autopsy was performed soon after death six days postoperatively.

Gross Pathology—Both the gallbladder and common duct (above ligature) were enormously distended, edematous, moderately thick walled and adherent to neighboring tissues. Bile could be seen in the dilated pancreatic duct. The pancreas appeared to be definitely larger than normal. The gallbladder bile was greenish brown with small masses of friable material. It contained both trypsin (activity of 0.8) and amylase (activity of 20) and cultures showed the presence of *B. coli* and gram negative and positive cocci.

Microscopic Findings—Gallbladder. The wall was considerably thickened with edema which was most apparent in the serosa. The vessels were dilated, the wall infiltrated with lymphocytes and a few polymorphonuclear cells and the mucosa devoid of epithelium except in the depths of the folds. The common duct showed the same changes. Pancreas. Both ducts and acini were widely dilated. There was however no necrosis or other change. Liver. Essentially normal except for moderate dilatation of the hepatic ducts. Kidneys. Normal.

Goat No. 1—Approx. age 15 months. **Diagnosis** Acute cholecystitis with gangrene perforation and localized peritonitis. Autopsy was performed 11 days later.

Gross Pathology—Tissues of the abdominal wall were bile stained. The gallbladder was dense, adherent to neighboring tissues. Between the stomach and gallbladder there was a small abscess of two or three ounces of thick fluid containing bile. This abscess communicated with the gallbladder which had perforated through a necrotic area. The gallbladder wall was very thick, translucent* and the external surface was milky white with a red overcast from dilated congested blood vessels. The mucosa was intensely inflamed.

The gallbladder contained thick greenish brown fluid and small pieces of brown friable material. The fluid was strongly positive for occult blood and from it were cultured *B. coli* and gram negative cocci. It was not examined for the presence of pancreatic ferments. The distal end of the common duct could not be identified.

Microscopic Findings—Gallbladder. The wall was very thick, the mucosa necrotic and the epithelium gone. There was profuse infiltration of the submucosa with polymorphonuclear leukocytes with formation of multiple abscesses. The remainder of the wall was considerably infiltrated with both polymorphonuclear and mononuclear cells. There was also moderate edema and fibroblastic infiltration.

* Upon emptying these gallbladders however they lost most of their slate green color. It seems that the gallbladder wall can be much thickened with edema and yet permit the green color to show through where is much less thickening of the wall with fibrous tissue renders them opaque.

Pancreas and kidneys Normal Liver Some fatty degeneration and a few interstitial polymorphonuclear leukocytes

Goat No 2—Approx age, 14 months *Diagnosis* Acute nonperforated gangrenous cholecystitis with local bile peritonitis

The common duct was ligated distal to the entrance of the pancreatic duct Twenty six hours later, the animal was moribund and, therefore was killed

Gross Pathology—The peritoneal cavity contained about four ounces of bile stained fluid The peritoneal surfaces were inflamed The gallbladder was moderately distended and dull in appearance It contained thin greenish brown fluid in which there were many small friable brown masses The fluid was sterile to culture, and contained both trypsin (activity of 2.4) and amylase (activity of 180) The extrahepatic ducts were moderately distended above the ligature

Microscopic Findings—Gallbladder The wall was thin and almost entirely necrotic There was no cellular infiltration and only slight edema Pancreas Essentially normal Liver and kidneys Essentially normal

GROUP II—Temporary Obstruction Distal to Junction of Pancreatic Duct

In some of the kids listed under permanent obstructions, temporary obstructions were intended but failed because the animals died too soon

Goat No 14—Approx age four months *Diagnosis* Acute nonperforated cholecystitis and acute pancreatitis with peritonitis

The common duct was obstructed temporarily with a ligature of plain catgut distal to the junction of the pancreatic duct Death occurred 19 days later

Gross Pathology—The tissues of the abdominal wall were bile stained The abdomen contained approximately 800 cc of bile stained fluid The peritoneal surfaces were inflamed The gallbladder was enormously distended and its walls widely adherent to neighboring tissues The wall was intact, moderately thickened and its mucous surface smooth with in many places, hemorrhagic areas The common duct was widely dilated above area of stenosis and its wall thickened It was not patent, the ligature had resulted in stenosis The gallbladder bile was greenish brown and contained many soft brown particles It contained both trypsin (activity of 1.5) and amylase (activity of 60) and *B. coli* and gram negative cocci in both smear and culture The pancreas was enlarged, firm, and tense

Microscopic Findings—Gallbladder The wall was markedly thickened with edema mainly in the serosa It was also partially necrotic and contained a few collections of leukocytes Bacteria were seen in the tissues Pancreas Almost entirely necrotic Bacteria were seen in the tissues Liver Essentially normal except for a few small collections of lymphocytes and polymorphonuclear leukocytes

Goat No 16—Approx age, 14 months *Diagnosis* Acute gangrenous cholecystitis with perforation

The common duct was ligated with plain catgut as a temporary ligature distal to the junction of the pancreatic duct The animal began failing 30 days later and was autopsied 32 days postoperatively

Gross Pathology—The gallbladder and common duct were distended and were densely adherent to surrounding tissues which walled off a cavity containing approximately six ounces of bile This fluid contained brown friable particles The cavity communicated with a perforation of the gallbladder The gallbladder bile contained both trypsin (activity of 2.0) and amylase (activity of 80), and cultures yielded *B. coli* and gram negative cocci

Both pancreas and liver appeared to be normal The common duct was almost completely occluded by the inflammatory process around it

Microscopic Findings—Gallbladder The wall was thickened considerably with edema mainly in the serosa It was partially necrotic and the epithelium was gone except for fragments in the depths of the folds Liver Some fatty degeneration otherwise normal Pancreas Essentially normal

Goat No 17—Approx age, 14 months *Diagnosis* Chronic cholecystitis

The common duct distal to the junction of the pancreatic duct was obstructed for 48 hours by the temporary occlusive method

Gross and Microscopic Pathology—Four weeks later, the gallbladder was explored and found buried in adhesions Bile was aspirated and found to contain both trypsin (a trace) and amylase (activity of 40) red blood cells 40–50, and leukocytes 1–15 per H.P.F. Cultures were sterile A biopsy was taken from the wall It showed a marked inflammatory reaction with edema, much leukocytic infiltration a loss of epithelium from the mucosa and some fibrosis

The animal was killed six months later The gallbladder was normal in size, buried in adhesions, opaque and grayish white in color, with dilated vessels over its surface It contained normal bile The mucosa was red and hyperplastic From the bile was cultured *B. coli* The common duct was patent but was enormously dilated above the point of temporary obstruction The regional lymph nodes were enlarged and there was edema of the gallbladder and neighboring tissues

Microscopic Findings—Gallbladder The wall was thickened with some edema, some fibrosis and extensive lymphocytic infiltration The mucous surface was devoid of epithelium except in the depths of the folds Common duct Changes similar to those of the gallbladder Pancreas Normal Liver Normal Kidneys Normal

Goat No 18—Approx age, 14 months *Diagnosis* Chronic cholecystitis

The common duct distal to the junction of the pancreatic duct was obstructed for 48 hours

Gross and Microscopic Pathology—Essentially the same as those of Goat No 17 From the gall bladder bile was cultured *B coli*

Goat No 19—Approx age, 14 months *Diagnosis* Chronic cholecystitis and cholelithiasis

The common duct was obstructed distal to the juncture of the pancreatic duct for 96 hours An exploratory operation was performed one month later

Gross Pathology—The gallbladder was buried in adhesions It was normal in size and the wall was edematous, very thick, opaque and grayish white in color Clear light green bile was aspirated It contained both trypsin (activity of 0.5) and amylase (activity of .40) From it were cultured *B subtilis* *B coli* and gram negative cocci

The animal was killed six months after operation The gallbladder was buried in dense adhesions It was thick, opaque and grayish white in color The common duct was patent but nevertheless, it was also enormously dilated and its wall thick Both gallbladder and common duct contained normal bile and, in addition many minute bile pigment stones From the bile, *B coli* was cultured Regional lymph nodes were large

Microscopic Findings—Gallbladder The wall was much thickened There was some edema and much fibrosis of all layers especially of the serosa The epithelium was hyperplastic and there were many submucosal collections of lymphocytes Common duct Changes same as those of the gallbladder Pancreas Normal Liver A few collections of leukocytes and some fatty degeneration Kidneys Normal

Goat No 20—Approx age 14 months *Diagnosis* Chronic cholecystitis and cholelithiasis

The experimental procedure was identical and the gross and microscopic findings essentially the same as those of Goat No 19 Bile aspirated at the exploratory operation one month after primary operation contained no trypsin but amylase (activity of 20) and in culture *B subtilis* *B coli* and gram negative and positive cocci Smears contained a few pus cells, crystals and debris Postmortem gallbladder bile contained *B coli*

Goat No 22—Approx age six months *Diagnosis* Acute gangrenous cholecystitis

The common duct distal to the juncture of the pancreatic duct was obstructed for six days The animal died two days later and was autopsied immediately

Gross Pathology—The gallbladder was adherent to neighboring structures and was moderately distended The wall was thickened, slightly injected edematous green in color and had no luster Although all extrahepatic ducts were moderately dilated, the common duct was patent The gallbladder bile was green but contained both trypsin (activity of 2.2) and amylase (activity of 160), and from it was cultured *B coli* Regional lymph nodes were large No definite cause of death was found

Microscopic Findings—Gallbladder The wall was thick very edematous and almost entirely necrotic except for fibroblasts The epithelium was gone and there was no cellular infiltration Sections from the other tissues were lost

Goat No 24—Approx age six months *Diagnosis* Chronic cholecystitis and cholelithiasis

The common duct was obstructed for six days distal to the juncture of the pancreatic duct Autopsy was performed two and one half months later

Gross Pathology—The gallbladder was densely adherent to edematous neighboring structures It was normal in size and the wall was milky green in color thick and edematous It contained normal bile and one large and two small bile pigment stones The bile contained only amylase (activity of 20), cultures of it were sterile The wall of the gallbladder contained *B coli* The extrahepatic ducts were much dilated and their walls were thickened The common duct was entirely patent

Microscopic Findings—Gallbladder The wall was moderately thick showing some edema and some fibrosis and moderate lymphocytic infiltration The mucous surface was mainly devoid of epithelium Common duct This presented the same changes Liver Some fatty degeneration Pancreas and kidneys Normal

GROUP III—*Temporary Obstruction Proximal to Junction of the Pancreatic Duct*

Goat No 25—Approx age three weeks *Diagnosis* Normal gallbladder

The common duct was obstructed between the junctures of the cystic and pancreatic ducts for 24 hours Death occurred from a respiratory infection five days later

Gross Pathology—The abdominal cavity was normal in appearance except for a few adhesions between the gallbladder and neighboring tissues The gallbladder was normal in appearance except that it was colored an abnormally dark shade of green The other viscera were normal The common duct was patent and not dilated but showed a narrow ring of thickening of its wall at the point where it had been occluded temporarily The gallbladder bile was normal in appearance Cultures of it and of the wall of the gallbladder were sterile It contained a trace of amylase but no trypsin

Microscopic Findings—Gallbladder Essentially normal, possibly slight edema of serosa Liver, pancreas, and kidneys Normal

Goat No 26—Approx age four weeks *Diagnosis* Normal gallbladder

The common duct was obstructed between the junctures of the cystic and pancreatic ducts for 48 hours The animal was killed 12 days later

Gross Pathology—The gallbladder was adherent to the duodenum and other tissues and was slightly distended as were the cystic and hepatic ducts There was some regional lymphadenopathy The common duct was narrowed by a ring of increased thickness of its wall at the site of temporary

occlusion, but it was patent. The other viscera were normal. The gallbladder bile was normal in appearance. Cultures of it gave no growth. It contained amylase (activity of 7).

Microscopic Findings—Gallbladder. Essentially normal, possibly slight edema of tissues and slight increase in subepithelial lymphocytes. Liver, pancreas, and kidneys. Normal.

Goat No 27—Approx. age, one month. *Diagnosis*. Partial biliary obstruction with subacute cholecystitis.

The common duct was obstructed between the junctures of the cystic and pancreatic ducts for six days. The animal was killed 14 days after operation.

Gross Pathology—The tissues were slightly icteric. The gallbladder, cystic and hepatic ducts were moderately distended, the ducts were tortuous, and their walls somewhat thickened by edema.

The gallbladder was grayish green in color, and there were many pericholecystic adhesions. The sentinel lymph nodes were very large. The common duct was almost occluded by a band of dense fibrous tissue at the site where temporary obstruction had been applied, it was patent, however. The duct above this level was moderately distended while below it was normal. The pancreas was enlarged and peculiarly soft in texture. The liver was swollen. The gallbladder bile was normal in appearance. From it was cultured the staphylococcus (probably a contaminant) and a diplococcus. It contained amylase (activity of 6.5) and lipase.

Microscopic Findings—Gallbladder. Moderate edema involving principally the submucosa and marked subepithelial infiltration of lymphocytes, these cells occurring in large collections. Liver. Intrahepatic ducts dilated and small scattered collections of mononuclear and polymorphonuclear leukocytes around ducts. Pancreas. Normal.

Goat No 28—Approx. age one month.

The common duct was obstructed between the junctures of cystic and pancreatic ducts for three days. The animal was killed 12 days later.

Gross Pathology—With the exception of some pericholecystic adhesions the gallbladder and other viscera were normal. The common duct was patent but was slightly narrowed by a band of increased thickness of its wall where temporary occlusion had been applied. The regional lymph nodes were enlarged. The gallbladder bile appeared to be normal. From it were cultured pneumococci. There was insufficient bile for examination for enzymes.

Microscopic Findings—Gallbladder. Essentially normal, slight subepithelial lymphocytic infiltration. Liver. Essentially normal. Pancreas. Normal.

GROUP IV—Permanent Obstruction Proximal to the Junction of the Pancreatic Duct

Goat No 12—Approx. age, one month. *Diagnosis*. Acute cholecystitis and acute hepatitis with multiple abscesses.

The common duct was ligated permanently, above the junction of the pancreatic duct. The animal died nine days later.

Gross Pathology—The tissues of the abdominal wall and of the viscera near the gallbladder were bile stained. The gallbladder was adherent to surrounding tissues. It was enormously distended and grayish green in color and contained thin greenish brown fluid in which there was considerable fine, soft brown material. This fluid contained no trypsin and only a trace of amylase (activity of 10). From it were cultured *B. coli* and gram negative cocci. The liver was swollen. The common duct was widely dilated above the ligation and normal below it. There were several large lymph nodes.

Microscopic Findings—Gallbladder. The epithelium was partially gone and the wall much thickened with edema and somewhat infiltrated with polymorphonuclear and mononuclear leukocytes. Common duct. This presented the same findings as the gallbladder. Pancreas and kidneys. Normal. Liver. There was an increase in interstitial fibrous tissue and this tissue contained bile pigment. There were many areas of collections of polymorphonuclear cells and areas of necrosis of liver cells.

GROUP V—Permanent Obstruction Distal to the Junction of the Pancreatic Duct Plus Cholecystostomy

Goat No 9—Approx. age one month. *Diagnosis*. Subacute cholecystitis.

The common duct was permanently ligated distal to its junction with the pancreatic duct, and a cholecystostomy was performed, with a catheter draining the gallbladder to the exterior. The catheter was extruded seven days later, an autopsy was performed on the following day.

Gross Pathology—There was considerable digestion of the skin for a wide area around the drainage tube. This became apparent within 24 hours after operation and was progressive. The gallbladder was buried in adhesions and was contracted. Its wall was thick and was grayish white in color. The pancreas and liver were normal in appearance and the extrahepatic ducts were not distended.

Microscopic Findings—Gallbladder. The wall was much thickened with edema of all layers but mainly of the serosa. There was also considerable lymphocytic infiltration and an increase in fibrous tissue. Pancreas. Normal. Liver. Slight interstitial edema.

Goat No 10—Approx. age, one month. *Diagnosis*. Subacute cholecystitis.

Cholecystostomy only was performed. The ducts were not disturbed. Aspirated gallbladder bile contained no traces of any enzymes and was sterile on culture. The animal was killed and autopsied eight days later.

Gross Pathology—The gallbladder and sinus tract were buried in adhesions. The gallbladder was contracted and its wall was thick and injected. The liver, pancreas, and extrahepatic ducts were normal in appearance. Regional lymph nodes were enlarged. There was only slight erosion and digestion of the skin around the drainage sinus.

Microscopic Findings—Gallbladder The wall was thickened by edema (mainly of the serosa) and by a marked lymphocytic infiltration and increase in fibrous tissue. The tissues also contained some polymorphonuclear leukocytes. The epithelium was hyperplastic. Pancreas Normal. Liver Normal.

Goat No 11—Approx. age, one month. *Diagnosis* Subacute cholecystitis.

The common duct was permanently ligated distal to the juncture of the pancreatic duct, and the gallbladder was drained externally by means of a catheter. Aspirated gallbladder bile contained a trace of amylase and no bacteria on culture. Death occurred six days later, no definite cause for it could be demonstrated.

Gross Pathology—The gallbladder was buried in adhesions and was thick walled and contracted. The extrahepatic ducts were not dilated. The pancreas appeared to be congested and the liver normal. Regional lymph nodes were enlarged.

Microscopic Findings—Gallbladder The wall was much thickened with edema, fibrosis and infiltration with lymphocytes and polymorphonuclear leukocytes. The cellular infiltration was mainly submucosal. The epithelium was hyperplastic. Pancreas The ducts were dilated and the blood vessels were distended. The gland was otherwise normal. Liver Essentially normal. Kidneys Essentially normal.

Goat No 21—Approx. age 15 months. *Diagnosis* Acute gangrenous nonperforated cholecystitis with bile peritonitis.

The common duct was ligated distal to the juncture of the pancreatic duct and a cholecystostomy was performed, draining the gallbladder to the exterior through a catheter.

Gallbladder bile procured at time of operation was negative for trypsin but positive for lipase and amylase (activity of 10). Microscopically, it was negative and gave no growth on culture. Bile aspirated from the tube 24 hours later contained both trypsin (activity of 2.0) and amylase (activity of 160). 40 leukocytes and 100 red blood cells per H.P.F. and gave no growth on culture.

Aspirated bile five days after operation, contained both trypsin (activity of 2.2) and amylase (activity of 140). Smears presented only amorphous material and crystals. Cultured were *B. coli* and gram negative cocci.

The tube fell out on the eighth day and drainage immediately ceased. The animal began to fail rapidly and was killed and autopsied three days later, 11 days after operation.

Gross Pathology—There had been considerable digestion of the skin around the sinus. The abdomen contained 600 or 700 cc of bile stained fluid and the peritoneal surfaces were slightly inflamed. This fluid contained both trypsin (a trace) and amylase (activity of 20), and was negative on culture. The gallbladder was distended, edematous, opaque and grayish white. Vessels on the surface were dilated. There was no demonstrable perforation of the gallbladder or leakage from the sinus. The gallbladder bile contained both trypsin (activity of 1.8) and amylase (activity of 140) and from it were cultured *B. coli* and gram negative cocci. The extrahepatic ducts were moderately dilated.

Microscopic Findings—Gallbladder The wall was thick, very edematous and partially necrotic. The mucous surface was almost entirely devoid of epithelium and the wall was moderately infiltrated with lymphocytes and contained a few polymorphonuclear leukocytes. Liver Normal. Pancreas and kidneys Tissue lost.

GROUP VI—Spontaneous Cholecystitis

Goat No 15—Approx. age 14 months.

Upon exploration this animal was found to have developed a cholecystitis spontaneously. Consequently no experimental procedure was undertaken. The animal was immediately autopsied.

Gross Pathology—The gallbladder presented a few adhesions, was normal in size and was dull red in color. Surface blood vessels were dilated. The wall was moderately thickened. The common duct was slightly dilated. Both gallbladder and ducts contained normal bile. The gallbladder bile contained amylase (activity of 20) and a trace of trypsin. Cultures yielded *B. coli*.

Microscopic Findings—Gallbladder The wall was moderately thickened, the epithelium slightly hyperplastic in some areas, absent in others, and there was some edema and moderate lymphocytic and fibroblastic infiltration. Common duct This showed similar changes. Pancreas and kidneys Normal. Liver Considerable fatty degeneration.

BRIEF ANALYSIS OF RESULTS OF EXPERIMENTS

Since the common duct in goats acts as a common conduit for both bile and pancreatic secretions, pancreatic juice normally is constantly present in the proximal end of the common duct. It would appear, therefore, that under normal conditions pancreatic juice either does not enter the gallbladder or if it does, it is innocuous. In an endeavor to investigate this question the gallbladder bile of five normal goats was examined for pancreatic enzymes. In three traces of trypsin and lipase were found, and in all, small amounts of

amylase Since many tissues of the body contain amylase, its presence in the gallbladder bile has no particular significance It has been shown by several investigators that pancreatic juice is innocuous until the enzymes have been activated by some substance Consequently unactivated enzymes could conceivably be present in the gallbladder without causing damage Thus, there is good evidence that pancreatic juice becomes a pathogenic factor in gallbladder disease only as a result of some other factor (probably stasis) which causes this juice not only to enter the gallbladder but also to become activated within this viscus

Quantitative determinations were made of amylase by the method of Myers and Fine, and of trypsin by the method of Gross Only qualitative determinations were made of lipase

Since the experimental results varied with respect to the site of obstruction produced in the common duct, the duration of the obstruction and the age of the experimental animals, the discussion is presented under the following headings

I OBSTRUCTION DISTAL TO PANCREATIC DUCT

The common duct was obstructed distal to the juncture of the pancreatic duct in 15 animals The obstructions in seven were permanent, and in eight temporary

(1) *Permanent Obstruction*—No animal survived obstruction longer than 11 days Three died within 26 hours The three that lived five days or longer showed evidence of jaundice

At postmortem examination, there was found, without exception, enormous dilatation of the gallbladder, cystic and hepatic ducts, and of the common duct above the site of obstruction (Fig 4) In five animals the gallbladder and ducts were adherent to the duodenum and other adjacent tissues and there were edema and very large lymph nodes in the gastrohepatic omentum

In four goats (Nos 2, 4, 7 and 8) there was present a bile peritonitis with no demonstrable perforation in the wall of the distended gallbladder and ducts Microscopically, the tissues of the walls of these gallbladders were either partially or entirely necrotic (Fig 5A) In two there was no inflammatory reaction, while in one there was moderate edema and in another much infiltration with lymphocytes and polymorphonuclear leukocytes

In one goat (No 1), the gallbladder had perforated with formation of a small abscess containing bile The wall of this gallbladder was very thick, opaque, grayish-white in color, with dilated vessels on its surface It was moderately edematous and extensively infiltrated with both mononuclear and polymorphonuclear leukocytes There were also areas in which the tissue was necrotic In the other two goats (Nos 5 and 13), there was considerable edema, particularly in the serosa, and in one considerable infiltration with inflammatory cells In all animals the epithelium was entirely missing or present only as small remnants in the depths of the folds

The gallbladder bile in all seven animals contained both amylase and

trypsin. It was sterile in three (Nos 2, 4 and 5), and contained *B. coli* and gram-negative and -positive cocci in four (Nos 1, 7, 8 and 13). There was also present much debris which had the appearance of digested blood.



FIG 4—A Enormous distention of the gallbladder resulting from obstruction of the common duct below the duct of Wirsung in Goat No. 14. This same degree of distention resulted from obstructions above as well as below, the juncture of the duct of Wirsung. Note edema, adhesions and lymphadenopathy.

B The gallbladder and ducts opened. (D) Duodenum. (L) Obstructing ligature with common duct much dilated above and normal below it. Note (N) areas of hemorrhage and necrosis in the wall. (B) Debris in gallbladder bile consisting of blood, necrotic tissue and inspissated bile.

Two goats were yearlings and five were approximately one month of age. In the two older animals the liver, kidneys and pancreas were normal.

In the five infants, there were gross and microscopic findings of acute pancreatitis with digestion necrosis in four (Fig 5C). The pancreatic ducts

were dilated in all five, and bile was seen in the ducts in three (grossly in two, and microscopically in one [Fig 5B]) The liver in three of this group contained multiple small abscesses

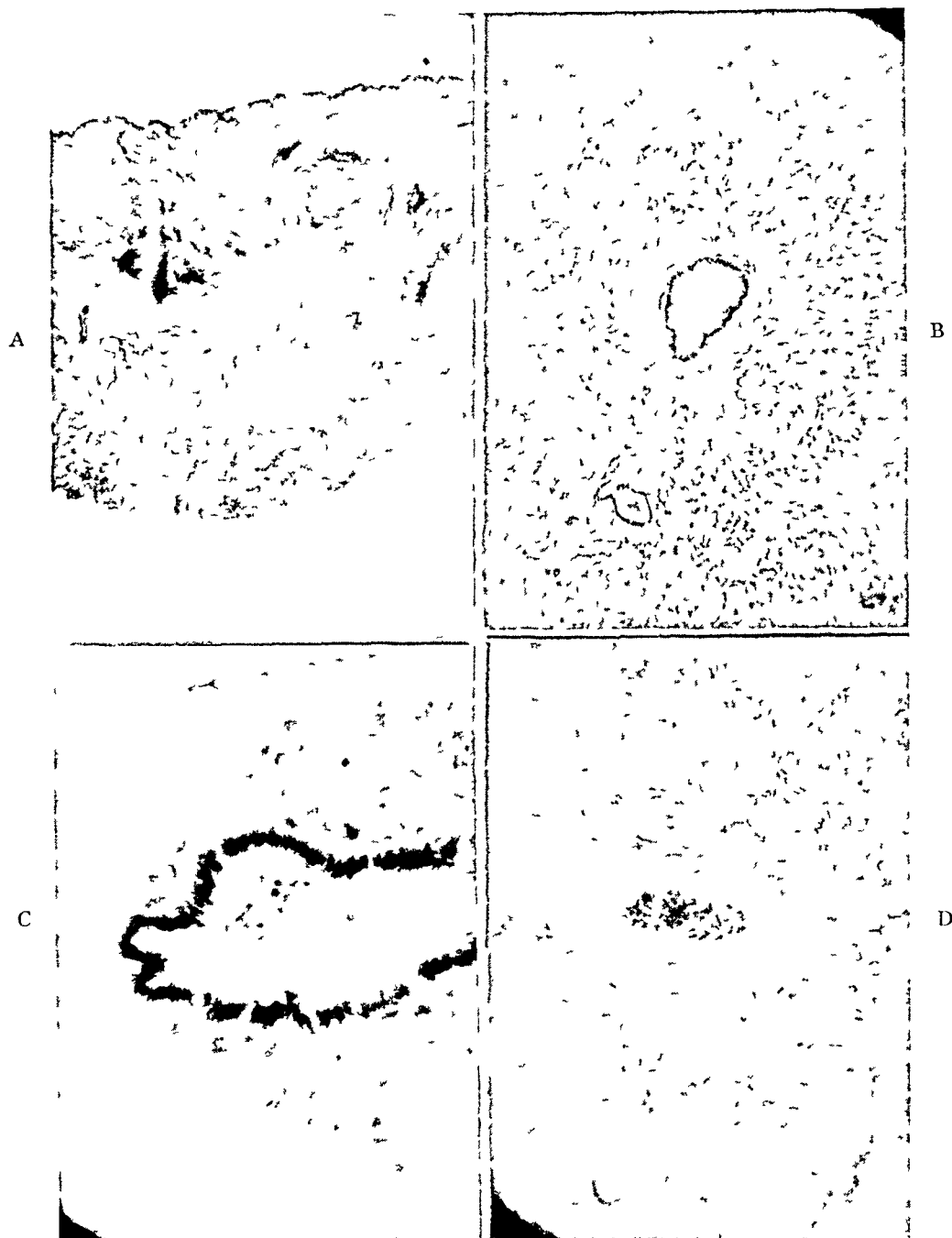


FIG 5—Goat No 4 Obstruction of the common duct distal to the juncture of the duct of Wirsung for three days produced gangrenous cholecystitis and pancreatitis with peritonitis

A Wall of gallbladder shows edema and aseptic necrosis. Note absence of lining epithelium, also absence of lymphocytic and leukocytic infiltration

B and C Area of pancreas showing a dilated duct filled with bile, with beginning necrosis of the acinar tissue around it

D Another area of pancreas showing necrosis of all tissues including necrosis of fat within the pancreas

COMMENT—It should be emphasized that (a) all gallbladders in this group contained pancreatic enzymes, evidence of hemorrhage into the viscus and loss of epithelium, (b) there was no evidence of infection in three,

(c) there was complete or partial gangrene of the wall of the gallbladder in five out of seven, with bile peritonitis in four and perforation in one, (d) the pancreas was unaffected by obstruction in the two older animals, and definitely damaged in the five infants (dilation of ducts in five, presence of bile in the ducts in three, and acute pancreatitis in four)

(2) *Temporary Obstruction* —It was found in the first group of goats used in this study, as reported above, that the very young ones developed acute pancreatitis in addition to cholecystitis, and died promptly after obstructing the distal end of the common duct. This did not occur in the two older ones of the group. Obviously, therefore, to study the effect of temporary obstructions the older animals had to be used. Consequently, all were four months and older. In two animals the distal end of the common duct was obstructed with a ligature of plain catgut, so that the duration of obstruction was not definitely known. In six, the obstructions were produced by the method illustrated in Figure 3 and were maintained from one to six days.

The two goats (Nos. 14 and 16), in which catgut ligatures were used, died from the results of the obstruction 19 and 32 days later. The ligatures had resulted in the formation of strictures which had caused persistence or recurrence of obstruction. Both had extreme dilatation of the gallbladder and biliary ducts above the sites of obstruction, which was complete in one and nearly complete in the other one. The wall of the gallbladder in both was much thickened with edema, and the bile contained both trypsin, and amylase and *B. coli* and gram-negative and -positive cocci. In the one which was four months of age, there was an acute, nonperforated gangrenous cholecystitis, with bile peritonitis, and acute pancreatitis with digestion necrosis. In the older one, 14 months of age, there was a perforation of the gallbladder, which was partially necrotic, and an adjoining abscess containing the same character of fluid as that found in the gallbladder.

A third goat (No. 22), in which the common duct was obstructed for six days, died two days after the obstruction was released. Although bile could be expressed from the ampulla by squeezing the gallbladder, both gallbladder and bile ducts were considerably distended. Gallbladder bile contained both trypsin, amylase, and *B. coli*. The wall of the gallbladder was almost entirely necrotic but contained a few fibroblasts.

The remaining five goats (Nos. 17, 18, 19, 20 and 24) lived with apparent good health, and were killed six months after the common duct had been temporarily obstructed. Three of them were explored four weeks after the original operation, and bile obtained by aspiration. It contained debris, crystals and white and red blood cells in addition to both trypsin and amylase. In one, it was sterile and from the bile of the other two, *B. subtilis*, *B. coli*, and gram-negative and -positive cocci were cultured. At postmortem examination, the gallbladders of all five goats were extensively adherent to the duodenum and other tissues and presented edema, fibrosis and lymphocytic infiltration of the walls in varying degrees. The wall in four (Fig. 7), was very thick and opaque, with dilated vessels on the surface, and in one, it was fairly thin and

GALLBLADDER AND PANCREATIC DISEASES

partially translucent. The lining epithelium was hyperplastic in three, and in one of these there was a papilloma. In two, the surface was devoid of epithelium in many areas.

In all five animals the gallbladder bile was normal in appearance, but in each instance *B. coli* was cultured from it or from the wall of the gallbladder. The bile contained only amylase, and in small amount, in the two specimens examined.

In three (Nos. 19, 20 and 24), of the five gallbladders, bile pigment stones were present. The stones in two animals were numerous and very small, and

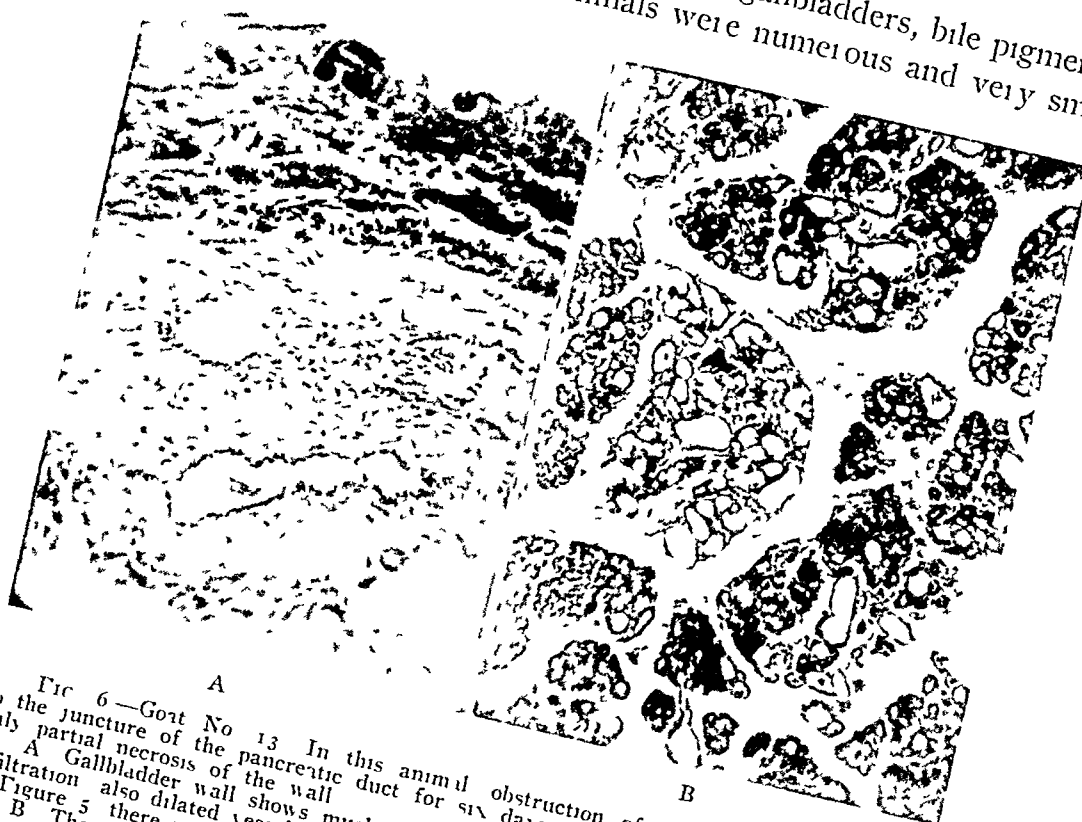


FIG. 6—Goat No. 13. In this animal obstruction of the common duct distal to the junction of the pancreatic duct for six days produced acute cholecystitis with only partial necrosis of the wall.
A. Gallbladder wall shows much edema, mainly of serosa, and some lymphocytic infiltration also dilated vessels and loss of most of the lining epithelium. In contrast to Figure 5 there is only partial necrosis of tissues.
B. The pancreas presents markedly dilated ducts and acini but no necrosis, also edema of interlobular connective tissue. On gross examination, bile was observed in the duct of Wirsung.

were present in both the gallbladder and the dilated common duct. The other gallbladder contained three stones, two of which were very small and one fairly large. Two of these specimens are shown in Figure 8.

In all of the animals, the pancreas and kidneys were normal and the liver normal except for slight fatty degeneration.

In every instance the common duct was greatly dilated despite the fact that there was no apparent obstruction and bile flowed freely into the duodenum. Contrary to the observations reported by Brackeritz, the common duct in these animals showed the same pathologic changes found in the gallbladder.

COMMENT.—Three animals in this group died of acute, gangrenous cholecystitis, one complicated by acute pancreatitis. In two, there developed a latent stenosis of the distal end of the common duct. Both pancreatic enzymes and infection were present in these gallbladders.

Five goats developed chronic cholecystitis with infection, and in three, stones formed

(3) *Permanent Obstruction with Cholecystostomy*—In each of three goats (Nos 9, 11 and 21), two, approximately one month of age, and one, about 14 months old, the distal end of the common duct was ligated with silk but, in addition, the gallbladder was drained through a catheter extending just beyond the skin surface. Bile aspirated at the time of operation was sterile on

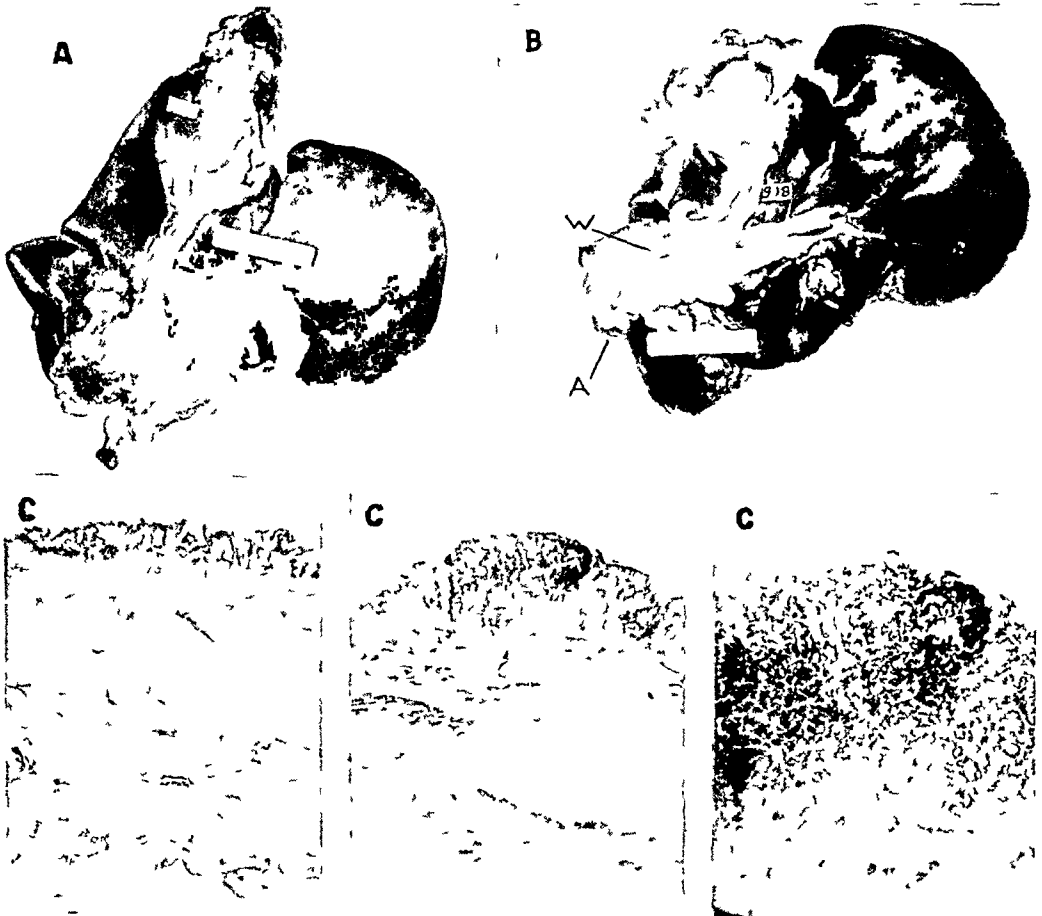


FIG 7—Goat No 18 Chronic cholecystitis six months after a temporary obstruction of the common duct distal to the juncture of the duct of Wirsung
A Gross specimen Note the thick opaque wall of the gallbladder, with engorged surface vessels, dilated cystic and greatly dilated common ducts
B The gallbladder and ducts opened Note the thick wall of the gallbladder and the enormously dilated common duct (W) Indicates the duct of Wirsung and (A) the ampulla of Vater
C The wall of the gallbladder is thick showing some edema fibrosis regenerated epithelium and extensive infiltration with lymphocytes (especially subepithelial) These sections taken from two areas of the wall show the histologic variation

culture and contained only traces of amylase. In one animal (No 21), samples of bile were collected aseptically 24 hours, and five days, after operation. Both specimens contained trypsin in addition to large quantities of amylase. In the first specimen there were 40 leukocytes and 100 red blood cells per H P F, and no bacteria on culture. The specimen obtained on the fifth day contained amorphous material, crystals and *B. coli* and gram-negative cocci on culture. This animal subsequently died with an acute, nonperforated gangrenous

cholecystitis, with bile peritonitis which followed three days after tube fell out and drainage ceased

In all three animals, the skin for a considerable distance around the wound became raw, presumably digested. This excoriation undoubtedly resulted from the action of pancreatic enzymes. This contention is supported by the fact that very little excoriation took place in a fourth animal (No. 10) which had a cholecystostomy without obstruction of the common duct. Drainage without obstruction was established in this animal for purposes of comparison. Grossly and microscopically, the gallbladder in this animal did not differ from that of two in which drainage was supplemented by obstruction of the common duct. In all of them, the gallbladder was contracted and the wall was very thick with edema, mainly of the serosa. It was infiltrated with lymphocytes, polymorphonuclear leukocytes and fibroblasts, and the epithelium was not only intact but appeared to be hyperplastic.

COMMENT—Although pancreatic enzymes traversed three of these gallbladders, in only one (No. 21) was there loss of epithelium and necrosis of the wall such as occurred in the previous group of animals in which obstruction of the common duct was not decompressed by drainage of the gallbladder. In Goat No. 21, however, the drainage sinus closed, with the result that the obstruction was no longer decompressed and stasis with distention followed. Thus, it appears that pancreatic enzymes are activated and attack the wall of the gallbladder only in the presence of stasis or that the wall becomes vulnerable only when it is distended. The pathologic changes found in the two contracted gallbladders were the result, no doubt, of trauma and infection.

OBSTRUCTION PROXIMAL TO PANCREATIC DUCT

The common duct was obstructed proximal to the junction of the pancreatic duct and distal to the junction of the cystic duct in five goats. The obstructions were made permanent in one animal with a ligature of silk, and temporary in four.

(1) *Permanent Obstruction*—The one goat in this group (No. 12) was one month of age. It died nine days after obstruction was established. There was a definite jaundice which was apparent in the tissues. The gallbladder and the ducts above the ligature were enormously distended. The gallbladder bile contained no trypsin and only a trace of amylase. *B. coli* and gram-negative cocci were cultured from it.

The walls of the gallbladder and common duct were edematous and infiltrated with mononuclear and polymorphonuclear leukocytes. It was partially devoid of epithelium but there was no necrosis of the other tissues of the wall. The liver contained focal areas of necrosis and multiple abscesses. The pancreas was normal.

COMMENT—Stasis in this animal accompanied by infection resulted in acute cholecystitis, hepatitis, and multiple liver abscesses. There was, how-

ever, no necrosis of the wall of the gallbladder and no pancreatitis as occurred with obstructions below the pancreatic duct in goats of this age

(2) *Temporary Obstruction*—The four goats (Nos 24, 26, 27 and 28) were approximately one month of age. The duration of the obstructions was 24, 48, 72, and 144 hours, respectively. The animal which was obstructed for 24 hours died from a respiratory infection five days later. The others were killed while apparently in good health 14 days after the operation.

With the exception of Goat No. 27, which will be discussed separately, the gallbladder, ducts, pancreas, and liver of each animal were essentially normal, both grossly and microscopically (Fig. 9). There were however in each

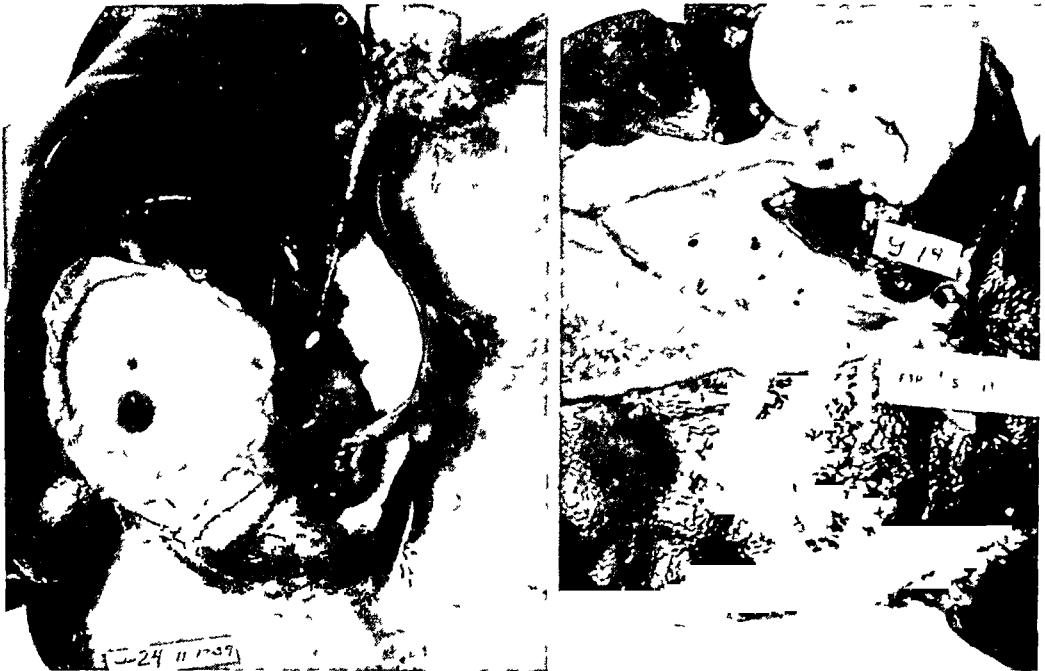


FIG. 8—Chronic cholecystitis with cholelithiasis which developed several months after temporary obstruction of the common duct distal to the juncture of the pancreatic duct in Goats Nos. 24 and 19. Note enormous dilatation of common duct and stones in both duct and gallbladder of Goat No. 19.

animal some pericholecystic adhesions, and adhesions between the duodenum and common bile duct. In each instance, the common duct was patent but was narrowed and its wall thicker than normal at the site where temporary obstruction had been applied. The gallbladder bile was normal in appearance and contained only amylase. It was sterile on culture in two goats and gave a growth of pneumococcus in one.

In Goat No. 27, an obstruction was maintained for six days, and the subsequent fibrosis of the wall of the duct at the site where obstructions had been applied had resulted in stenosis which was almost complete. Above this level the common duct and the hepatic and cystic ducts were much distended as was the gallbladder. The gallbladder bile was normal in appearance and contained only amylase. From it were cultured the staphylococcus (possibly a contaminant) and a diplococcus. The liver was swollen and the intrahepatic ducts dilated. The wall of the gallbladder was thicker than normal, the lining epi-

thelium intact and normal, and there was no necrosis of tissue. The subepithelial tissues were moderately edematous and densely infiltrated with lymphocytes. The pancreas was normal. The gross and microscopic appearances of this gallbladder are shown in Figure 10.

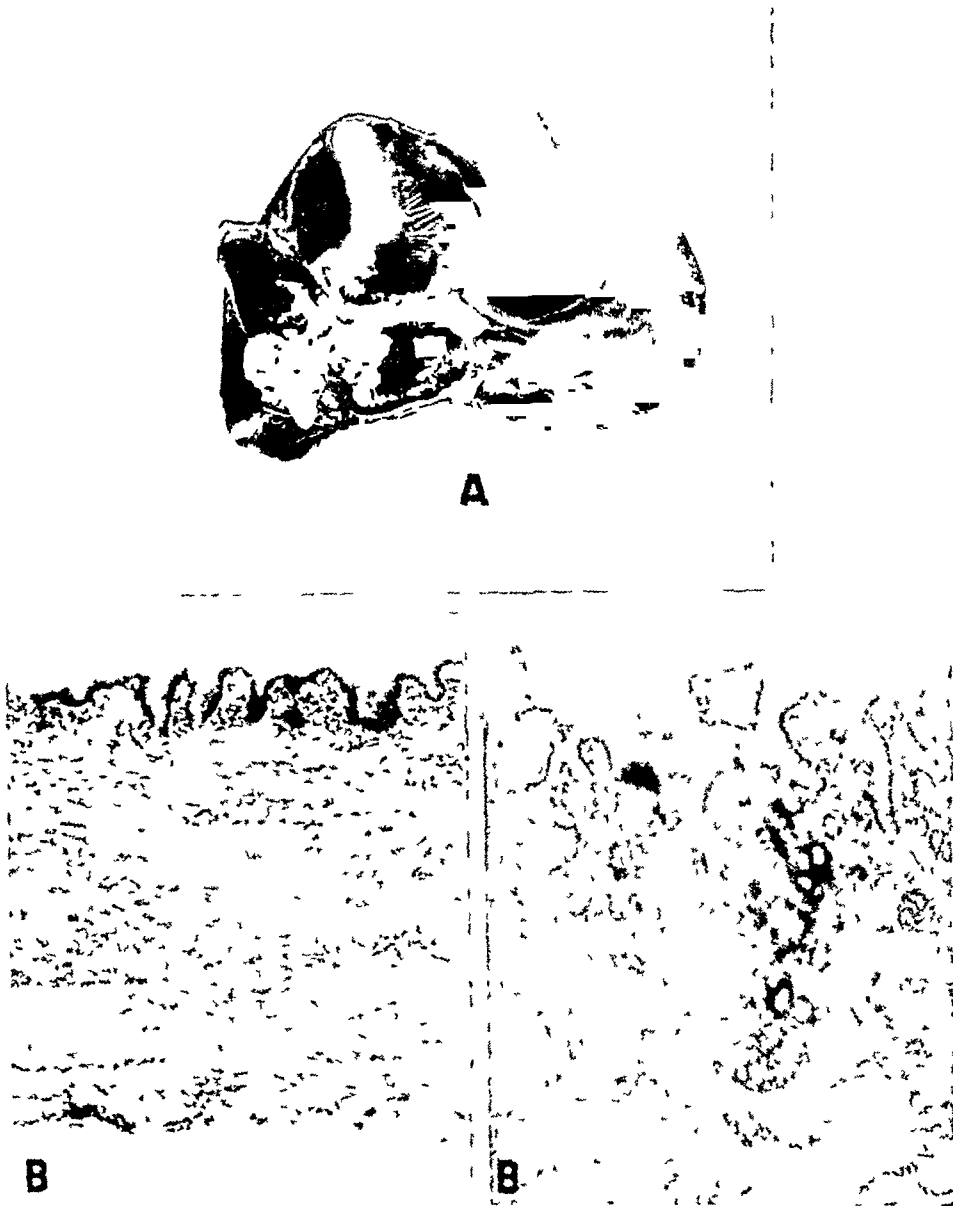


FIG. 9—Goat No. 26. The common duct was obstructed for 48 hours proximal to the juncture of the pancreatic duct and distal to the cystic duct. The animal was killed 12 days later.

A. Gross specimen showing an essentially normal gallbladder.

B. Microscopically also the wall of the gallbladder is essentially normal. Temporary biliary stasis produced no permanent damage.

COMMENT—The gallbladders of animals in this group were subjected to temporary stasis of bile without the reflux of pancreatic secretions. With the exception of the one animal, in which partial obstruction persisted, there was a return of the biliary tract to an essentially normal condition. There was no loss of epithelium or necrosis of the wall such as occurred in gallbladders subjected to the reflux of pancreatic juice in addition to stasis. The pancreas was unaffected.

III NATURAL CHOLECYSTITIS

In the course of the investigation one of the yearling goats (No 15) presented, at operation, a gallbladder with the gross appearance of cholecystitis. *B. coli* was cultured from the wall of the gallbladder. The findings were essentially the same as those of the experimentally produced chronic cholecystitis with the notable exceptions that there were no pericholecystic adhesions and no dilatation of the common bile duct. The ducts and liver were normal in appearance and no mechanical explanation for the cholecystitis could be found.

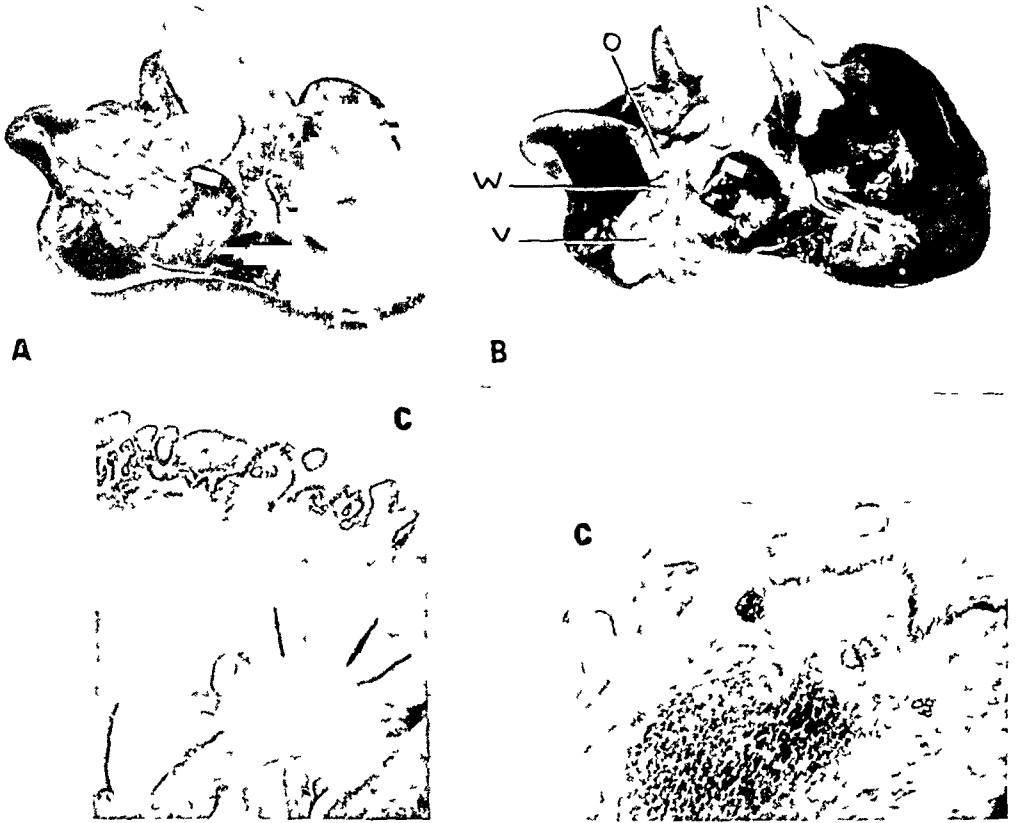


FIG 10.—Goat No 27. Common duct was obstructed for six days proximal to the duct of Wirsung and distal to the cystic duct. Scarring at site of obstruction resulted in partial permanent stenosis.

A and B. Gross specimen shows moderate distention of the gallbladder and of the ducts proximal to the area of stenosis. (O) Site of obstruction. (W) junction of duct of Wirsung, (V) impullus of Vater. Note that the common duct below the stenosis is normal.

C. The wall of the gallbladder shows moderate edema and much lymphocytic infiltration of the subepithelial tissues. Despite prolonged biliary stasis the lining epithelium is intact and normal, and there is no necrosis of the tissues as resulted from obstructions distal to the junction of the duct of Wirsung. This gallbladder was infected cholecystitis resulting from stasis plus infection.

DISCUSSION AND CONCLUSIONS

From these experimental data it may be concluded that neither stasis of bile nor the reflux of pancreatic juice as a single factor was productive of cholecystitis. When combined, they invariably produced permanent pathologic changes in the gallbladder. By their combination, there was produced acute aseptic cholecystitis with complete or partial necrosis of the wall of the gallbladder. The immediate pathologic changes, it is believed, were chemically

induced and not the result of infection, for the reasons that they lacked histologic features characteristic of infection and that cultures from the gallbladder bile and wall were sterile in most instances. In several animals there was an associated bile peritonitis without perforation of the wall of the gallbladder and, in two, a perforation with localized peritonitis. Precisely the same pathologic pictures occur in man, and we share the conviction of Wolfe that the pathogenesis is the same.

In the older animals, which survived this initial acute reaction, which we have reason to believe included some necrosis of the wall of the gallbladder, there developed chronic gallbladder disease not unlike that of man. No gallbladder subjected temporarily to both stasis and reflux of pancreatic secretions reverted, with recovery, to its previous normal condition. All developed permanent pathologic changes. Despite the fact that the mucous membrane completely or partially regenerated in most instances, evidence of chronic inflammation persisted. Since bacteria were cultured from all of these chronically inflamed gallbladders, it seems probable that superimposed infection was an important contributing factor in this subsequent development of chronic cholecystitis.

Unquestionably, the bile pigment stones, which developed in three animals, formed as an indirect, if not direct, result of stasis and reflux of pancreatic secretions. In addition to precipitation from altered relations of the chemical constituents of the bile, these gallbladders contained much debris, consisting of blood from hemorrhage and of fragments of sloughed mucous membrane. Theoretically, these particles provided nuclei around which precipitated elements could collect. This debris, always present in the bile for a few weeks after the initial insult from stasis and pancreatic reflux, gradually disappeared, and the bile became clear and normal in appearance.

Temporary biliary stasis alone (in absence of pancreatic reflux) had no destructive action upon the wall of the gallbladder and was productive of permanent pathologic changes in only those gallbladders in which there were positive cultures to indicate that infection had supervened. In the absence of infection, gallbladders subjected to temporary stasis promptly reverted to their previous normal states.

Thus, it may be concluded that stasis played an essential and fundamental rôle but not the active one in the production of cholecystitis and stones. Apparently it merely created circumstances favorable to the damaging activity of pancreatic enzymes and of bacteria. In other words, cholecystitis resulted from stasis plus either the reflux of pancreatic secretions or infection or a combination of the three factors.

The same factor which induced stasis caused the reflux of pancreatic juice, and, in turn, distention of the gallbladder. Thus stasis either activated the pancreatic enzymes or, by distending the wall of the gallbladder, rendered it vulnerable to the action of the enzymes and to infection. It is our belief that these same factors are responsible for chronic cholecystitis in man.

In our animals, stasis was induced by obstructing the common duct. There

is much evidence that temporary obstruction of the common duct in man may result from spasm of the sphincter of Oddi and from reverse peristalsis in the duodenum, in addition to stones or other obstructing factors within the common duct or at the ampulla.

The occurrence of acute pancreatitis in five of the younger goats, following obstruction of the common below the pancreatic duct, was an interesting incidental development. The pathogenesis of acute pancreatitis has been attributed to the reflux of bile into the pancreas with the assumption that the bile activates the pancreatic enzymes within the pancreas itself. This contention, however, has been contested by some contrary evidence. Thus, it has been shown by Haims and Diagstedt that in the dog the secretory pressure of the pancreas is greater than that of the liver. It has been reasoned that under these circumstances it is unlikely that bile would enter the pancreas. This begs the question of relative secretory pressures to explain the presence of bile in the pancreas, and the development of pancreatitis in the very young goats and the failure of its development in the older ones. It is probable that, in the former, the secretory pressure of the liver exceeded that of the pancreas. In two of the very young goats the presence of bile in the pancreatic ducts was observed grossly and, in one, microscopically.

It has been shown that filtered bile does not activate pancreatic enzymes but that bile unfiltered or containing bacteria does. This may serve to explain the absence of pancreatitis in one of the goats in which bile could be seen in the pancreatic duct. But it also seems reasonable to assume that the refluxed bile observed in the pancreas of the other two goats was a pathogenic factor in the production of acute pancreatitis in these animals.

BIBLIOGRAPHY

- ¹ Albeau-Fernet, M. Les hypotheses de la lithase biliaire. *Gaz Med de France*, **43**, 3, 1936.
- ² Andrews, E., Schoenheimer, R., and Hrdina, L. Etiology of Gallstones. *Arch Surg*, **25**, 796, 1932.
- ³ Andrews, E., Hrdina, L., and Dostal, L. E. Etiology of Gallstones. *Arch Surg*, **25**, 1081, 1932.
- ⁴ Aronsohn, H. G., and Andrews, E. Experimental Cholecystitis. *Surg, Gynec and Obstet*, **66**, 748, 1938.
- ⁵ Blaa, A. Studien uber Gallenperitonitis ohne Perforation der Gallenwege. *Arch f klin Chir*, **109**, 101, 1918.
- ⁶ Bundschuh, E. Zur perforationlosen Gallenperitonitis. *Arch f Chir*, **161**, 549, 1930.
- ⁷ Cameron, A. L., and Noble, J. F. Reflux of Bile Up the Duct of Wirsung Caused by an Impacted Biliary Calculus. *J A M A*, **82**, 1410, 1924.
- ⁸ Clairmont, P., and Haberer, H. Gallige Peritonitis ohne Perforation der Gallenweg. *Mitt d Grenzgeb d Med u Chir*, **122**, 154, 1911.
- ⁹ Colp, R., Gerber, I. E., and Doublet, H. Acute Cholecystitis Associated with Pancreatic Reflux. *ANNALS OF SURGERY*, **103**, 67, 1936.
- ¹⁰ Cooper, G. H., and Illingworth, C. F. S. Experimental Study of the Factor of Biliary Stasis in the Production of Gallstones. *Surg, Gynec and Obstet*, **46**, 658, 1928.
- ¹¹ Dolkart, R. E., Jones, K. K., and Brown, C. F. G. Chemical Factors Concerned in the Formation of Gallstones. *Arch Int Med*, **62**, 618, 1938.
- ¹² Dostal, L. E., and Andrews, E. Etiology of Gallstones. *Arch Surg*, **26**, 258, 1933.

- ¹³ Drury, E R, McMaster, P D, and Rous, R Observations on Some Causes of Gallstone Formation Jour Exper Med, 39, 403, 1924
- ¹⁴ Dragstedt, L R, Haymond, H E, and Ellis, J C The Pathogenesis of Acute Pancreatitis Arch Surg, 28, 232, 1934
- ¹⁵ Elman R Personal communication
- ¹⁶ Elman, R and Graham, E The Pathogenesis of "Strawberry" Gallbladder Arch Surg, 24, 14, 1932
- ¹⁷ Feldman, M, Morrison, S, Carr, C J, and Krantz, J D Contribution to the Etiology of Gallstones Am Jour Digest Dis and Nutrit, 4, 223, 1937
- ¹⁸ Greene, C H, Walters, W, and Fredrickson, C H The Composition of the Bile Following the Relief of Biliary Obstruction Jour Clin Invest, 9, 295, 1930
- ¹⁹ Harms, E Pressure Readings in Bile and Pancreatic Duct Systems Arch f Klin Chir, 147, 637, 1927
- ²⁰ Ivy, A C, and Walsh, E L Observations on the Etiology of Gallstones Ann Int Med, 4, 134, 1930
- ²¹ Lueth, H C Studies on the Flow of Bile into Duodenum and the Existence of a Sphincter of Oddi Am Jour Physiol, 99, 237, 1931
- ²² Mann, F C, Foster, J P, and Brimhall, S D The Relation of the Common Bile Duct to the Pancreatic Duct in Common Domestic and Laboratory Animals Jour Lab and Clin Med, 5, 203, 1919
- ²³ Mann, F C, and Giordana A S The Bile Factor in Pancreatitis Arch Surg, 6, 1, 1923
- ²⁴ Phemister, D B, Aionsohn, H G, and Pepinsky, R Variations in Cholesterol, Bile Pigment and Calcium Salts Contents of Gallstones Formed in Gallbladder, and in Bile Ducts, with the Degree of Associated Obstruction ANNALS OF SURGERY, 109, 161, 1939
- ²⁵ Phemister, D B, Day, L, and Hastings, A B Calcium Carbonate Gallstones and Their Experimental Production ANNALS OF SURGERY, 96, 595, 1932
- ²⁶ Popper, H Pankreassaft in den Gallenwegen Arch f klin Chir, 175, 660, 1933
- ²⁷ Ravdin, I S, Johnston, C G, Austin, J H, and Riegel, C Studies of Gallbladder Function Am Jour Physiol, 99, 638, 1932
- ²⁸ Riegel, C, Ravdin, I S, and Rose, H Studies of Gallbladder Function Jour Clin Invest, 16, 67, 1937
- ²⁹ Rous, P, McMaster, P D, and Drury, D R Observations on Some Causes of Gallstone Formation Jour Exper Med, 39, 77, 97, 403, 1924
- ³⁰ Westphal, K Die Durch Dyskinese der Ausführungsgänge bedingten Pankreasfermentschädigungen an den Gallenwegen und der Leber Ztschr f klin Med, 109, 55, 1929
- ³¹ Whitaker, L R The Mechanism of the Gallbladder and Its Relation to Cholelithiasis J A M A, 88, 1542, 1927
- ³² Idem The Relation of Biliary Dysfunction to Lithiasis New York State Jour Med, 34, 221, 1934
- ³³ Wolfer, J A The Role of Pancreatic Juice in the Production of Gallbladder Disease Surg, Gynec and Obstet, 53, 433, 1931
- ³⁴ Idem Pancreatic Juice as a Factor in the Etiology of Gallbladder Disease Surgery, 1, 928, 1937
- ³⁵ Idem Further Evidence That Pancreatic Juice Reflux May Be Etiologic Factor in Gallbladder Disease ANNALS OF SURGERY, 109, 187, 1939

DISCUSSION —DR CHARLES P BAKER (Omaha, Neb) Doctor Bisgard has shown you the gross pictures of the livers and gallbladders taken from our animals, and I wish briefly to discuss the microscopic findings which we have in these animals

The first group is the one in which the ligature was temporarily placed above the duct of Wirsung and so we have only the bile obstruction In part

of these animals the bile was sterile and in part cultures grew streptococci. Sections of the gallbladder walls in this group show collections of leukocytes in the subepithelial region and edema of the wall. There was no evidence of necrosis of the wall in this group.

In the second group of animals the ligature was placed below the pancreatic duct and the animals were killed in two to three days following the procedure. In these animals the gallbladder wall was digested, and sections show no structure remaining normal in the wall. There were no collections of leukocytes in the wall and the mucous membrane was entirely gone. In part of these animals the pancreatic sections showed bile in the pancreatic ducts and there was digestion of the pancreatic acini and fat in many areas. Apparently the ferments for fat and protein digestion had been activated. The picture of the pancreas is similar to that which we see clinically in so-called acute pancreatitis. The liver in a number of these animals had small abscesses distributed throughout its substance.

In the third group of animals the common duct was temporarily ligated below the pancreatic duct and the animals were killed several months later. In this group of animals the epithelial lining of the gallbladder mucosa was intact. The walls in this group were thickened by edema and fibrosis, and there were uniformly present large collections of leukocytes in the subepithelial region of the wall. It was in this group of animals that calculi were found in several instances.

DR JOHN A. WOLFER (Chicago, Ill.) I am indeed pleased to hear this report by Doctor Bisgard because, December 5, 1930, I presented the results of some experimental work on this subject before the Chicago Surgical Society. It did not seem to impress anyone present at that meeting, in fact, I could not convince my audience that the theory had any merit whatsoever. Since that time, however, it has gained proponents.

Recently, I made a survey of the literature reporting the results of anatomic studies on the relationship of the terminal common duct to the pancreatic duct. It indicates that in eight studies covering 652 cases, a common pathway between the pancreatic and common ducts was found in 43.4 per cent of cases. This would indicate that in approximately 45 per cent of all individuals there is a common pathway between the pancreatic and common ducts, thus allowing an interchange of duct contents, *i.e.*, bile to pass into the pancreatic system and pancreatic juice into the biliary ducts and gallbladder. Many cholangiograms, when carefully studied, reveal a visualization of the pancreatic ducts as stated by Doctor Bisgard. We are able to verify this observation.

For our experimental work we used the dog, placing a cannula into the major pancreatic duct and a T-tube into the common duct. These two were connected externally, using a glass observation bulb so as to be able to determine whether the preparation was satisfactory. Since the secretory pressure of the pancreas is greater than that of the liver, the flow in a successful preparation was always from the pancreatic to the biliary side, revealing a turbid opalescent fluid in the observation bulb. In order to determine whether the pancreatic juice that was flowing into the common duct ever entered the gallbladder, India ink was introduced into the observation bulb in one animal. Five days later the animal was explored and the mucosa of the gallbladder was found stained black as were also the contents of the gallbladder.

Aside from the preparation just described, we injected pancreatic juice directly into the gallbladder, also into the common and cystic ducts in some of the experimental animals. Figure 1 shows the gallbladder of an animal 24 hours after the injection of 15 cc. of pancreatic juice into the cystic duct.



FIG 1—Photomicrograph (X35) of the wall of the gallbladder of a dog that died 24 hours after the injection of 15 cc of pancreatic juice into the cystic duct. The wall is much thickened, 4mm, and shows diffuse necrosis, with edema. No viable structures can be seen. (Courtesy of Surgery, Gynecology and Obstetrics.)



FIG 2—Photomicrograph (X85) of the gallbladder wall of a dog that was killed 20 days after the injection of 20 cc of pancreatic juice into the gallbladder. The mucosa has partly sloughed away. There is shown extensive infiltration of inflammatory cells into the submucosa and muscular layers, and infiltration and thickening of the serosa.



FIG 3—Photomicrograph (X195) of the serosa of the gallbladder of a dog that died seven days after a choledochopancreatic intubation. On the left can be seen a dilated blood vessel with perivascular infiltration. There is present extensive necrosis, with edema, and some cellular infiltration.

The gallbladder was gray in color and the wall 4 Mm in thickness. There was complete necrosis of the wall, with edema. No viable structure or cells could be seen. Such a response was encountered on several occasions, the process often being associated with bloody bile stained fluid in the peritoneal cavity.

With the introduction of pancreatic juice into the biliary duct system of gallbladder, varying pathologic changes were found in the wall of the gallbladder of the individual cases. In a case in which 20 cc. of pancreatic juice had been injected into the gallbladder, 20 days later a study of the gallbladder revealed a partial sloughing away of the mucosa with an infiltration of inflammatory cells into the remaining portions of the mucosa, the submucosa and muscular layers (Fig 2). The microscopic appearance of the wall of the gallbladder is almost identical with one that Doctor Bisgard has shown.



FIG. 4.—Photomicrograph ($\times 45$) of the mucosa of the gallbladder of a dog killed 187 days after a choledochopancreatic intubation had flowed nine days. There are shown hypertrophy and hyperplasia with cyst formation, and extensive inflammatory cell infiltration.

In another instance in which the animal died seven days after a choledochopancreatic intubation, there was found extensive necrosis, with edema, also cellular infiltration with perivascular infiltration in the wall of the gallbladder (Fig 3). In every instance that the experiment was successful, pathologic changes were found in the wall of the gallbladder ranging from acute and extensive necrosis to partial necrosis and regenerative hyperplastic changes. The longest time interval observed was in an animal killed 187 days after a choledochopancreatic intubation had existed for nine days. There were found hypertrophy and hyperplasia with retention cyst formation and extensive inflammatory cell infiltration of the mucosa of the gallbladder (Fig 4).

There seems to be no question, at least not in my mind, that pancreatic juice reflux may explain many of the bizarre pathologic pictures frequently observed in the operating room. My curiosity was aroused, in 1928, when I encountered a large, tense and cyanotic gallbladder in the presence of an acute pancreatitis. The gallbladder was removed and, much to my surprise, cultures from the walls of the gallbladder and its contents were sterile. It was obvious that there must be some unrecognized process at work, a process not infectious in nature, that was the basis of the profound changes found. That observation led to the experimental work that was reported ten years ago. I am indeed pleased to see the results of Doctor Bisgard's work upon the same subject and quite naturally I am gratified by his conclusions.

DR EVARTS A. GRAHAM (St. Louis, Mo.) I think this has been a most interesting paper beautifully presented. I am not quite certain however, whether Doctor Bisgard wishes to give the impression that all cases of cholecystitis are due to this mechanism or only a small percentage of them. I have been interested in Doctor Wolfer's ideas on this subject ever since he proposed them, and I would say that I think that the idea is a very attractive one. I should like to feel that the explanations are as simple as Doctor Wolfer and Doctor Bisgard, now, would have us believe. On the other hand, there are certain things that, from a purely logical standpoint, make it difficult for me to accept this idea as an explanation of many cases of cholecystitis.

These ideas briefly, are. In the first place, this idea would make the origin of cholecystitis due to an anatomic anomaly which presumably exists

from the time of birth or even in fetal life, if you will. Pancreatic secretion becomes active in late fetal life. How does it happen, then, that children—babies—who have this deformity escape cholecystitis if it is due merely to this anatomic arrangement, and why is it, therefore, that cholecystitis is a disease of middle life, or beyond, almost entirely? Now, again, Doctor Wolfer calls our attention to the fact that approximately 45 per cent of people have this anatomic arrangement, but 45 per cent of the people do not have severe cholecystitis—on any way near that percentage!

Again, Doctor Bisgard introduces the element of stasis as an important factor. Of course, Aschoff has, for many years, emphasized the importance of stasis as a factor in the production of cholecystitis. I am not sure whether or not Doctor Bisgard means obstruction when he speaks of stasis. That is, of course, a very different thing, namely, obstruction is a very different thing from stasis. Now, as a matter of fact, people who have stasis in the gallbladder are the type of individuals who are less likely to have cholecystitis. "Uncle Sam" does not have cholecystitis, but "John Bull" does. By cholecystography, one can demonstrate that "Uncle Sam" has stasis but "John Bull" does not. The individual with the long gallbladder is the one who has stasis, and frequently this gallbladder is to be seen, by cholecystography, not to empty for 36 or 48 hours. The patient who has gallbladder disease is the one who has the cholecystographic shadow that appears as a circle up under the ribs. "John Bull" I mentioned. Heavyweight wrestlers and pugilists represent types of individuals who are likely to have gallbladder disease. Yet they empty more promptly than what we consider the normal gallbladders, therefore, it is difficult for me to understand, really, that the explanation of cholecystitis can be so simple as this idea which is proposed and promulgated this morning by Doctor Bisgard, which he would have us believe.

Now I am pleased, however, I must say, to see this additional evidence in favor of the idea that cholecystitis is not, by any means, always an infectious process. I used to think that it was, but I think that the evidence is becoming more and more overwhelming that it is not.

There is another point which I think is interesting to consider in connection with this presentation. It is not a question of. Can you produce cholecystitis by getting pancreatic juice into the gallbladder? Anyone would accept that. I cannot see that there would be any doubt about that, but the point is, of course, does human cholecystitis, as we see it, occur in this way? Now you can produce cholecystitis by introducing lots of things into the gallbladder. Mann showed, many years ago, that an intravenous injection of Dakin's solution resulted in a gangrenous cholecystitis, but certainly he did not mean to imply that human cholecystitis is caused by people going around getting intravenous injections of Dakin's solution, and that is, Mr. President, the enigma which it seems to me these studies present.

DR. J. DEWEY BISGARD (Omaha, Neb., closing). There is a very strong growing feeling that infection is not the initial etiologic factor in the majority of the cases of cholecystitis. It has been shown, of course, and repeated experimentally by Andrews and many others, that it is practically impossible to infect the normal gallbladder. They have introduced various types of bacteria into the gallbladder and have failed to initiate an infection unless the gallbladder was also damaged or had been previously damaged. So we believe that the physical or chemical changes that took place in the presence of stasis in these animals damaged the gallbladder wall and rendered it vulnerable to either bacteria or enzymes. Now we are not attempting to apply these observations directly to the disease in humans, but we can show in our animals,

subjected to stasis alone, that the gallbladder returned to a fairly normal condition. Stasis gallbladders that did not become infected returned to normal. If they became infected, they developed the picture of subacute or chronic cholecystitis.

It has been demonstrated repeatedly, particularly by Colp in a large series of cases, that one can frequently recover pancreatic enzymes from the gallbladder. I think he recovered them in as many as 20 per cent of the cases in which the common duct was drained, showing that the mechanism can take place. As to the frequency with which it takes place, I have no idea. I do believe, however, that it is the mechanism responsible for most of the cases of acute gangrenous cholecystitis that we see.

THE QUESTION OF DRAINAGE FOLLOWING CHOLECYSTECTOMY^{*}

IRVIN ABELL, M D

AND

IRVIN ABELL, JR, M D

LOUISVILLE, KY

THE WIDE DIVERGENCE of opinion regarding the wisdom or even the propriety of omitting drainage after cholecystectomy due to reported instances of bile leakage with resultant peritonitis, has led us to review a series of 500 consecutive cases subjected to operation during the decade from 1930 to 1940. For purposes of brevity and facility of discussion cholecystectomy alone, carried out in the absence of surgical attack upon other portions of the biliary tract or adjacent organs, other than the coincident removal of the appendix, will be considered. The questions upon which decision is sought are: Is it permissible to eliminate drainage, and is it always necessary to drain even after "ideal cholecystectomy"?

In our earlier experience, drainage by a rubber tube or a plicated strip of gauze enclosed in rubber tissue, designated as a "cigarette drain," was employed in all cases. Undesirable sequelae following such practice were occasionally noted, and consisted chiefly of infection, delay in wound healing, and persistence of sinuses for days beyond the time required for the healing of the undrained wounds. We finally came to the practice of discarding drainage in cases conforming to certain criteria, and it is to this group to which we invite your discussion.

It has been our practice to employ drainage in every case showing gangrene, marked pericholecystic edema, inflammation or abscess, demonstrable common duct and pancreatic disease, spillage of bile from the gallbladder or cystic duct, the visible presence of bile in the beds of the gallbladder and cystic duct, abnormal relationship of artery, vein and ducts which do not permit of satisfactory identification and control, and in the instances in which the separation of pericholecystic adhesions has left appreciable denuded surfaces. It is our belief that the drain employed in the presence of these indications—tube, cigarette or Penrose—should be left *in situ* for a time sufficiently long to permit of canalization that will insure a route of exit for wound secretions and discharges, a period of time which our experience indicates to be not less than six or seven days. The practice of removing the drain piecemeal at intervals of 24 to 48 hours has, at times, resulted in retention and accumulations in the depth of the wound, permitting the occurrence of that which their employment was designed to prevent and materially prolonging convalescence. The employment of drainage in the conditions

* Read before the American Surgical Association, St. Louis, Mo., May 1, 2, 3, 1940.

mentioned is so universal as to require no further comment, but when one approaches the elimination of drainage in "ideal cholecystectomies" opinions and practices show divergence

The wide variations in the anatomic relations of the cystic artery and duct, hepatic artery, portal vein, common and hepatic ducts have been repeatedly described, and the presence of accessory ducts in relation to the cystic and hepatic ducts as well as ducts of embryonal origin in the perimuscular coat of the gallbladder has been noted. Flint, in an article upon the "Abnormalities of the Right Hepatic, Cystic and Gastro-Duodenal Arteries, and of the Bile Ducts," in the *British Journal of Surgery* of April, 1923, reported finding accessory hepatic ducts in about 15 per cent of his dissections. The ducts of Luschka found on the perimuscular hepatic surface of the gallbladder, which while not communicating with the gallbladder do often anastomose with the bile ducts in the liver, have been estimated by some to be present in 6 per cent of all cases.

The above findings, together with reported failures of closure of the cystic duct after ligation, offer to many surgeons an imperative demand for the employment of drainage in every case. Is the surgical importance of these anomalies overestimated by some and underestimated by others? Are these anatomic variations susceptible of recognition at operation? Is there a technic which gives any assurance of such recognition, at the same time affording a degree of safety in occluding aberrant and accessory ducts? Instances of drainage from the stump of the cystic duct as late as six to eight days after ligation have been observed. Do these bear any relation to the method of ligation or to the degree of pressure or infection in the common duct, and are there any reliable criteria upon which security of obliteration or of danger of reopening may be predicated? Beyond the generally accepted indications for the employment of surgical drainage elsewhere, these are the problems about and upon which hinges the choice for or against drainage following cholecystectomy.

Briefly, the "ideal cholecystectomy" we have in mind, and in which we have eliminated drainage, is presented by the case in which the common duct is normal in size and gives no evidence of concretions or periductal inflammation, in which the head of the pancreas shows no increase in size or consistence, in which the relations of the cystic duct, the common duct and the cystic artery can be readily defined by dissection with satisfactory identification of each, and in which the gallbladder can be separated from its bed by sharp dissection without exposure of liver tissue. In such instances the cystic duct, with or without the cystic artery, depending upon their relations, has been doubly ligated with No. 1 chromic catgut ligatures—one, a transfixion ligature placed proximal to the clamp in which the duct is held, the other, a mass ligature at the site of the grasp of the clamp. The connective tissue bed of the gallbladder is closed by a continuous suture of chromic catgut welded on a curved intestinal needle, beginning at the point of ligation of cystic duct and proceeding to the outermost point of the gallbladder bed,

after which it is carried back to its starting point, transfixing the tissues not tightly held in the first layer. In this technic no liver tissue is exposed and the cellular tissue of the gallbladder bed is firmly closed. We have at times covered the stump of the cystic duct with peritoneal flaps, as a rule, however, omitting this feature without noting any difference in convalescence.

Of the 500 cases reviewed, 109 were drained and 391 were not drained. Acute cholecystitis was present in 74, chronic and subacute, in 426. Calculi were present in 408, absent in 92. Of the acute cases, 34 were drained and 40 not drained. Of the chronic and subacute, 75 were drained and 351 not drained. There were ten deaths in the series, a mortality of 2 per cent, two occurring in the 109 drainage cases, and eight in the 391 nondrainage cases.

Bronchopneumonia alone accounted for five deaths—two on the third, one on the fourth, one on the fifth, and one on the twelfth postoperative day. The patient dying on the fifth day presented a marked ileus, arousing the suspicion of an intra-abdominal etiology independent of the toxemia from the pulmonary lesion. Autopsy revealed the peritoneal cavity free of pathology.

Dehiscence occurred in two cases. One, not drained, exhibiting persistent singultus, beginning on the third postoperative day, developed a dehiscence on the thirteenth day, and died of a terminal bronchopneumonia on the seventeenth day, the other, drained, developed a primary bronchopneumonia, and suffered a dehiscence on the fifth day, and died on the eighth day. Both abdomens, at time of resuturing, were free of evidence of leakage or of peritonitis.

One patient died of acute hepatic toxemia after removal of a gangrenous gallbladder. One died of mesenteric thrombosis, symptoms appearing on the tenth, exploration being made on the eleventh, and death occurring on the twelfth postoperative day. Permission for autopsy was refused, the origin of the thrombosis remaining conjectural. The tenth fatality occurred on the third postoperative day as a result of myocardial failure and pulmonary edema.

In our earlier experience, a cigarette drain was the one commonly employed, bile-tinged drainage during the first 24 to 72 hours was occasionally noted. In the present series, employing a more meticulous technic, and using a Penrose tube as a drain, bile-tinged drainage, in scant amount, has rarely been observed. All of the patients analyzed in this series were private ones, and since many of them elected to remain in the hospital for a longer time than was actually necessary, no accurate estimate of the required hospitalization can be given for the two groups. It is our impression, however, that the Penrose drain increases the time of hospitalization in but few instances.

Our experience in this series, as well as in that of previous years, leads us to believe that the anomalies of the cystic artery and of the bile ducts do not have the surgical significance which has been accorded them by some observers. While we believe that the reported cases of such anomalies demand a particularly careful operative technic in all instances, we are by no means sure that the one we employ gives complete assurance against leakage from

unrecognized accessory ducts or reopened cystic ducts. We are not so optimistic as to believe that what has happened to others may not happen to us. The presence of infection in the common bile duct may not always be recognized by inspection and palpation, and, when present, may be the cause of failure of obliteration of the cystic duct with consequent leakage. We may have been fortunate in relying upon the criteria mentioned in protecting us from such a disaster. In any event, we have not seen, in this series or in the experience of previous years, any of the complications which have been ascribed to closure without drainage. The valid arguments which may be offered in favor of the elimination of drains are the avoidance of adhesions which their presence necessarily engenders, and the occasional delay in wound healing induced by infection, with prolongation of convalescence and resultant weakened scars. That such advantages do or do not outweigh proven dangers, and as to whether or not in selected cases a careful technic offers a reasonable margin of safety in avoiding the latter, is to be proved by collective rather than individual experience.

DISCUSSION —DR JOHN A. WOLFER (Chicago, Ill.) I am indeed happy to hear Doctor Abell present his thesis at this meeting. We have for years, in the group I work with, omitted drainage in the majority of cases following cholecystectomy. The question seems to revolve about the possibility of leakage from the cystic duct which is ligated at the time of operation, therefore, infection and sundry other aspects need not be considered at this time.

In 1927-1928, in order to determine what happens to a ligated cystic duct, we carried out some experimental work upon the dog. It may be pertinent to mention again the results of that work, since it has a direct bearing upon the subject before us at this time.

It was noted that 24 hours after operation, the stump of the cystic duct was covered with an exudate consisting of red blood cells and coagulated serum, so that it was not visible after the lobes of the liver and other adjacent structures that had prolapsed over it had been separated. Microscopic examination of the duct stump revealed compression of the tissues within the grasp of the ligature and beginning cellular disorganization of the stump, distal to the ligature. At the end of four days, the exudate containing many young connective tissue cells was well fixed to the duct stump, completely covering it. When the exudate was separated from the duct stump, it was noted, very frequently, that the ligated duct was very brittle, so that it would fracture at the site of ligation with the slightest brush with the tip of the finger, revealing an open lumen without any evidence of repair. Microscopic examination of the duct stump showed necrosis of the duct wall distal to the site of ligation, under the ligature, and for a few millimeters proximal to it, proximal to this, the duct wall appeared normal (Fig. 1). This would indicate that the ligature deprived the duct wall of its blood supply, since the portion of the duct under the ligature, and distal to it, had been dissected free at the time of ligation and the only blood supply available was that within the wall of the duct. The cystic duct wall does not repair itself as does a blood vessel by a reparative process within the duct wall, as can be noted in Figure 1. By the end of seven days, the exudate is firmly fixed to the duct structures and can be separated only with difficulty. Microscopic examination of the exudate shows many young and maturing connective tissue cells. Examination of the duct stump clearly indicates the site of ligation and complete necrosis distal and

a few millimeters proximal to the site of ligation. It also illustrates the absence of any reparative process within the duct wall so that a disruption at the site of ligation, at this time, will lead to a communication between the lumen of the proximal duct and the exterior (Fig. 2)

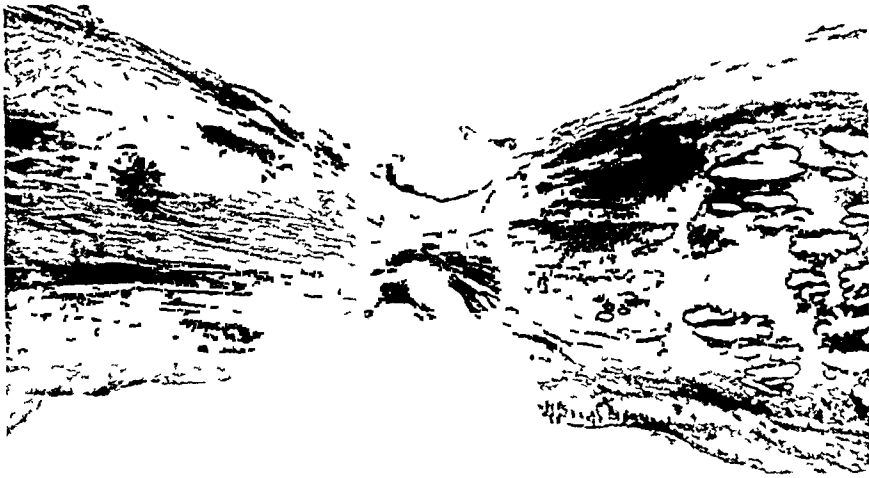


FIG. 1—Photomicrograph of the cystic duct stump at the zone of ligation on the fourth day. This shows the zone of proximal as well as distal necrosis. (Low power)

As this process is followed along, it can be noted that the exudate finally becomes well organized, and completely obliterates the duct stump by burying the necrotic portions in a mass of well-organized connective tissue. This was observed at the end of 33 days.



FIG. 2—Photomicrograph of the cystic duct stump on the seventh day. This clearly indicates the extensive necrosis distal to the ligation, also beneath and proximal to the ligation, and demonstrates that at this period, no reparative changes have taken place in the duct to occlude its lumen.

It was also noted, in the experimental animals into which we inserted drains, that if anything was placed about the cystic duct stump that interfered with the deposition or laying down of the exudate, which later became the defensive and reparative mechanism, healing was prevented or markedly delayed. If drains were inserted and then removed on the third or fourth day,

the exudate which had already formed around the duct was disturbed and did not cover the stump, so that a definite time-interval had to elapse for a further, and sometimes inadequate exudate to form, thus interfering with and delaying repair

It would seem that this experimental work warrants the conclusion that in those cases in which there is no reason for drainage other than a fear of leakage from the cystic duct, it is distinctly contraindicated. We employ drainage following cholecystectomy very, very rarely, I would say in not more than 5 per cent of our cases, and, so far, we have had no reason for regrets

DR HENRY F GRAHAM (Brooklyn, N Y) I have believed for many years in the general principle that it is better to omit drainage in operations upon the gallbladder whenever possible but have carefully avoided any attempt to influence others to adopt this practice because of the obvious dangers of closing the abdomen without a drain when one is necessary. It now seems fair, however, to give our statistics. Over a period of about ten years, we have accumulated a series of consecutive cases without drainage. There have been 346 in all, with 12 deaths, or a mortality of 3.47 per cent. Please note that these are not consecutive cases, but they are consecutive cases which were *not* drained. In the last 200 gallbladder operations, up until March 12, 1940, no drain was employed in 62.5 per cent, or, conversely, we drained one-third of the cases.

It is our belief that none of the deaths occurred as the result of lack of drainage. Postoperative accumulation of bile did occur in two cases but both of these recovered. Closure of the abdomen without a drain does diminish postoperative pain, gives more prompt and better healing of the wound, and favors the deep breathing which we all so much desire following gallbladder operations.

I agree with Doctor Wolfer that the insertion of a drain is often responsible for the biliary discharge which is sometimes seen in a wound and which the surgeon says is positive proof that a drain was needed. If the drain were not inserted, the tissues would collapse and you would get peritoneal exudate and adhesions, as he mentioned, and you would not have biliary discharge at all.

In considering these statistics which I have mentioned, if they seem high to you at all, I should like to remind you that we have an active ambulance service at the Methodist Hospital. We serve a large tenement house district with many Italians. This may affect our mortality somewhat.

DR HARRY B ZIMMERMAN (St Paul, Minn) I was very much interested in Doctor Abell's presentation and also in Doctor Wolfer's experimental work. If you will notice in Doctor Wolfer's last slide there is a canalization of the cystic duct. This section was taken five or six days after the ligature had been applied. If one considers the abdomen as a closed hydrostatic bag, then all pressures, at any one time, would be equal, and leakage from a viscus would occur only when the pressure within the viscus compared to pressure without the viscus was great enough to rupture its wall. If the differential pressure were always the same this would not take place.

Years ago, when we used rigid tubes, we made the atmosphere communicate directly with the weakest part of the duct. Consequently we nearly always had bile leakage. At present, when one uses a Penrose drain the closed container is not sufficiently spoiled so that leakage is not so likely to occur, but should the drain be left in long enough, so that its tract becomes thoroughly canalized with a rigid inflammatory wall the tube situation will

again obtain, and there will be a point of positive differential pressure at the end of the canal at a time when the duct wall was weakest and rupture of the duct could very well occur. Should there be a diastasis of the muscular abdominal wall six days after operation, the same situation would occur. Should there be positive pressure throughout the entire abdomen, except in the neighborhood of the hernia, leakage would occur.

Therefore, in the operation for removal of the gallbladder, in order to prevent bile leakage it is important to have accurate closure of the abdominal wall by means of an incision so designed as to make a hernia least likely—and no drain! If there is a possibility that one may get an early hernia and a leakage of bile, obviously it is best to have a fistula.

I would say the ideal situation is a ligated duct and a closed abdomen. If there is any doubt about this, use a drain that could establish a fistula but, also, that it should be so placed, and the abdominal wall sutured about it so tightly, that the closed container is not spoiled and that there is the least likelihood of a differential pressure at the point at which the duct was ligated.

DR CHARLES G MIXTER (Boston, Mass.) I should like, briefly, to call attention to the value of immediate cholangiography in determining the safety of closure without drainage. Perhaps the most potent cause of leakage is back pressure through the cystic duct from impediment to the outflow. If a renal catheter is placed in the cystic duct, the valve is obtained in withdrawal of bile, and one can determine whether or not a cholangitis exists. Secondly, if the common duct is visualized and immediate, free flow into the duodenum is demonstrated, one is quite sure that the element of back pressure due to impediment of the outflow of the bile into the duodenum is eliminated. I believe that in that selected group where some of us feel we can close the abdomen without drainage, cholangiography at the operating table gives us an added factor of safety.

NEUROGENIC DISTURBANCES OF THE COLON AND THEIR INVESTIGATION BY THE COLONMETROGRAM^{*}

A PRELIMINARY REPORT

JAMES C WHITE, M D

MAX G VERLOT, M D ,

AND

OTTO EHRENTHEIL, M D

BOSTON, MASS

FROM THE NEUROSURGICAL SERVICE OF THE MASSACHUSETTS GENERAL HOSPITAL, BOSTON, MASS

IN 1927, Rose¹ described a method of observing the reaction of the bladder to filling. Many communications of interest have appeared since, which have been recently reviewed in McLellan's² excellent monograph. Cystometry has become a most useful aid in studying the behavior of the bladder. Eight years before Rose's first publication, Joltain, Bauffe, and Coope³ proposed a method of measuring the filling pressure of the large intestine. They described only a few such attempts and drew no important conclusions. So far as we are aware, nothing more had been done in studying the physiology of the colon by colonmetry until the method was independently rediscovered and put into routine use in the study of neurologic disturbances in defecation at the Massachusetts General Hospital, two years ago.

METHOD—The apparatus employed is very simple, and consists of a vertical glass tube manometer one meter in height, connected on one side to an intravenous drip apparatus and on the other to a rectal tube (Fig 1). The reservoir is filled with water at body temperature and the tubing cleared of air. The base line of the manometer is adjusted so that the meniscus of the water column is at the zero mark when the tip of the rectal tube is level with the patient's anus. The tube is then inserted a few inches within the rectum and held in this position by adhesive tape. It is best to have the patient lying on his back with his head comfortably supported on a pillow. When the anal sphincter is paralyzed the connection can be made water-tight by using a Foley bag type of catheter with the balloon inflated to 100 cc (Fig 1, insert). The same device is also useful when the test has to be made through a colostomy opening. Once the apparatus is adjusted, water is allowed to flow into the rectum at a constant rate of approximately 100 cc per minute. The patient is instructed to report any sensation of "gas," "urge to defecate," or cramp-like pain, with its location and intensity. Extreme care must be exercised in any patient with an insensitive colon or with colonic diverticula lest a perforation be produced by overdistention.

The test is best performed a number of hours after the last meal and when

^{*} Read before the American Surgical Association, St Louis, Mo, May 3, 1940

the bowel has been recently evacuated. A correct interpretation cannot be drawn if the patient has been given a cathartic or narcotic drug.

We wish to point out that the colonmetrogram does no more than measure the tone, reflex irritability, and sensitivity of the colon as a whole. It gives a good indication of the competence of the anal sphincter, but fails to give a true

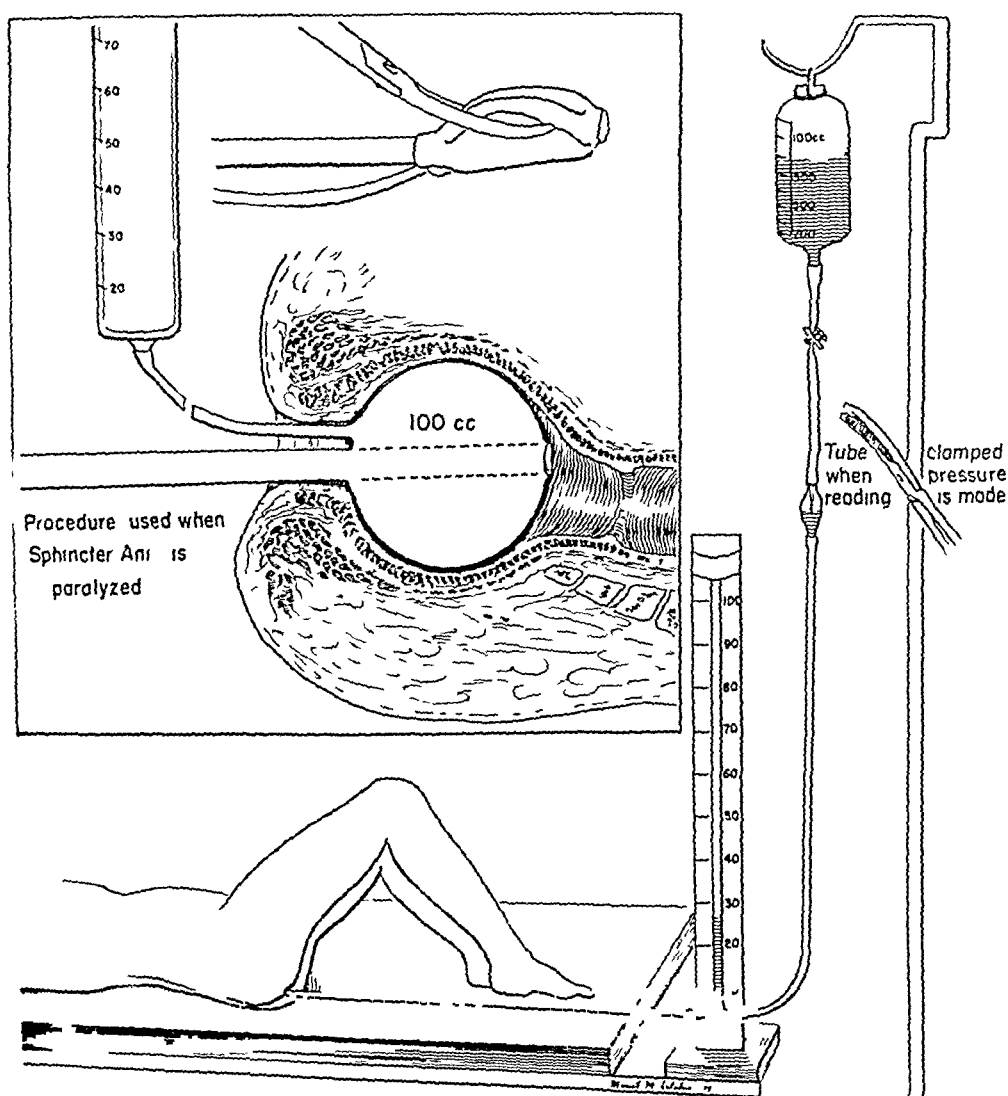


FIG. 1.—Apparatus and technic of colonometry

indication of the expulsive power of the rectum, which is dependent to a large degree on the contractile force of the abdominal musculature and the diaphragm. The integrative mechanism of the rectum, sphincter ani, and perineal muscles must be studied by the more elaborate methods which have been described by Denny-Brown and Robertson⁴. Furthermore, localized functional abnormalities in the rectum, sigmoid, or higher portions of the colon cannot be differentiated. It would appear, however, that neurologic disturbances usually affect the colon as a whole, and for this reason we have found the colonmetrogram to be a simple and valuable method of testing the nervous activity of the viscus.

MATERIAL—This investigation has been focused on patients with disease, injury, or operative lesions of the brain, spinal cord, cauda equina, or pelvic

nerves which may cause an alteration of function or sensation in the large bowel. Sixty-seven colonmetrograms have been performed in a series of 40 patients.

RESULTS—The normal colonmetrogram closely resembles the cystometrogram, except for the fact that a fourfold larger volume of water is usually required for filling*. Figure 2 illustrates the comparative volume of fluid which is required to fill the normal bladder and colon. Whereas the normal adult bladder holds from 300 to 500 cc at a maximal comfortable capacity, the colon holds between 1,500 and 2,000 cc. Both hollow viscera have

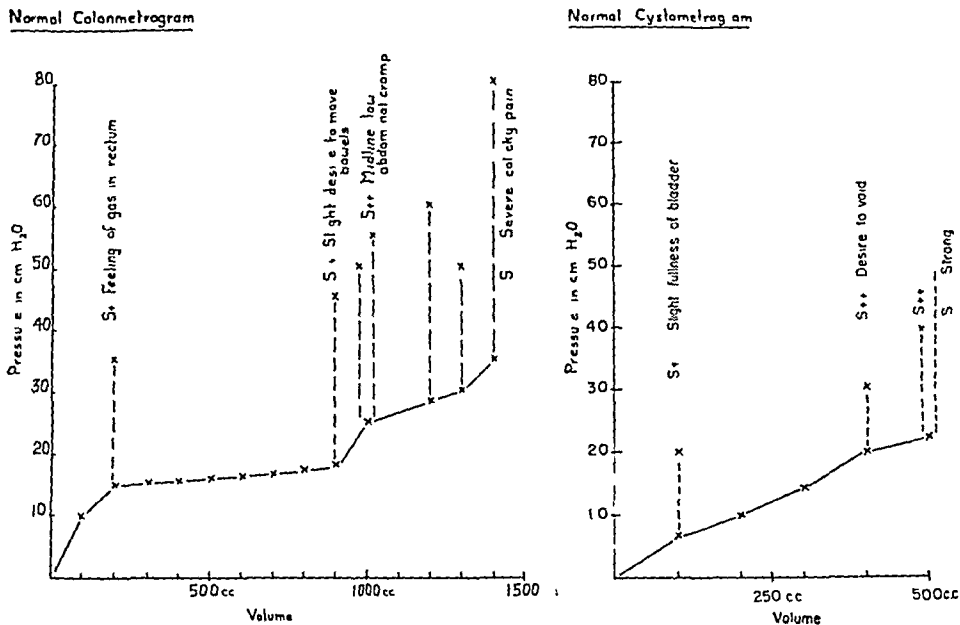


FIG. 2—The normal colonmetrogram and cystometrogram

a relatively similar basic tone and react to stretching by intermittent reflex attempts to empty. This is shown by peristaltic contractions which last a few seconds and send the intravesical and intracolonic pressures up to from 30 to 90 cm. A sensation of fullness is produced in the normal colon, as in the bladder, when the pressure reaches 30 cm, whereas a contraction which raises the column above 50 cm becomes distinctly uncomfortable. The basic tone is seen to rise rather steeply as the normal capacity is approached, and peristaltic waves occur with increasing frequency until a state of tetanic contraction is reached. At this point, fluid usually leaks out around the catheter. The pressure-volume measurements can be combined with barium fluoroscopy if a thin barium mixture is used that will not clog the manometer. The contraction peaks are then seen to correspond to mass waves of peristalsis which sweep the fluid down into the distal colon. Haustrial segmentation does not produce any waves visible in the manometer, as no fluid is forced down the canal.

* With slow filling of the colon there is always a possibility of leakage through the ileocecal valve. Short of fluoroscopic examination, this unknown factor cannot be controlled, but we have no evidence that it is of importance.

The smooth muscle in the colon, as in the bladder, reacts to stretch stimuli by reflex contraction (Denny-Brown and Robertson⁴) Colonmetry in patients with various types of neurologic lesions, therefore, brings out changes which are characteristic of the level at which the nervous system is involved These phenomena are identical with those observed in the bladder (McLellan²), and quite similar to alterations in the tendon reflexes

Typical cases which illustrate the effect of injury to the various segmental levels of the nervous mechanism of defecation are appended It must be borne in mind that this is a preliminary report and that colonmetry has not been

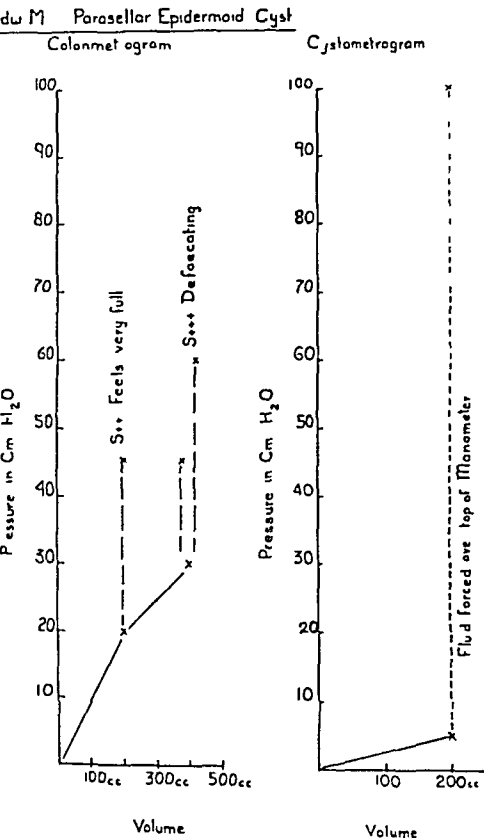


FIG 3—Case 1 Hypertonia of colon and bladder seen in the case of a brain tumor which compressed the hypothalamus and cerebral peduncles

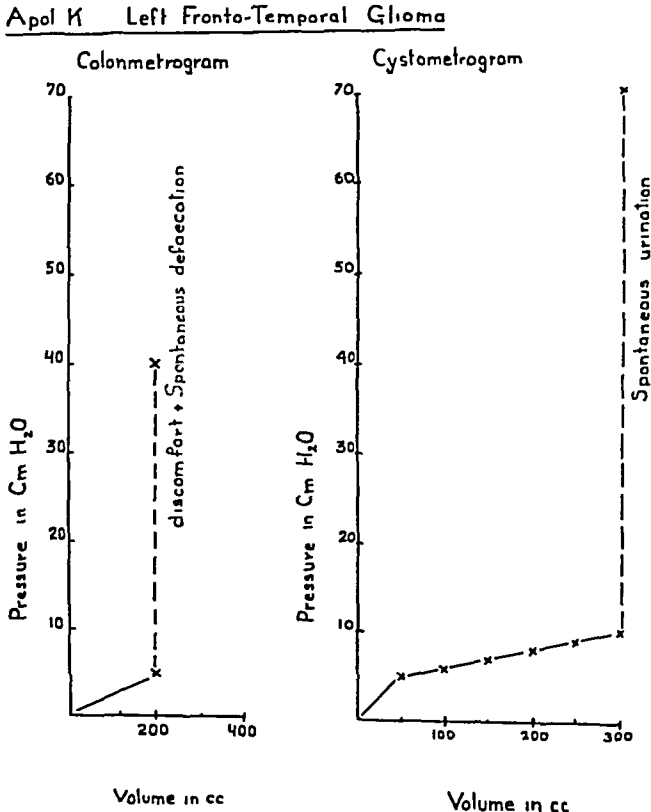


FIG 4—Case 2 Hypertonia of colon and bladder observed in an extensive tumor of the left frontal lobe

undertaken on a large enough series of cases to draw final conclusions But the evidence at hand is entirely consistent and the findings quite similar to data obtained from the bladder by a great many investigators Since conclusions can be drawn only from complete and clearly defined lesions of the nervous system, such as can be produced in the experimental animal, this report is necessarily based upon the relatively small proportion of our total cases which fulfill these criteria

I LESIONS IN THE BRAIN

Case 1—Edward M, male, age 15 Epidermoid cyst in floor of left middle fossa, with extension across the midline and compression of hypothalamus and cerebral peduncles (verified at autopsy)

The patient was intelligent and cooperative. There was no clinical evidence of injury to the autonomic centers in the hypothalamus. Both his cystometrogram and colonmetrogram curves are reproduced in Fig 3, and reveal an extraordinary hypertonicity of both bladder and colon, with entirely normal sensation. On a second occasion, the colonmetrogram was repeated with barium and the filling observed fluoroscopically. On account of the intense muscular activity of the sigmoid, barium could not be forced up beyond the rectosigmoid.

Case 2—Apol K, male, age 57. Left frontotemporal glioma. Diagnosis was established only by ventriculography, as the patient subsequently died without operation or postmortem examination.

The patient was aphasic, apraxic, and had undergone a pronounced change in personality, so that his cooperation could not be counted on with certainty. Right hemiparesis and a suggestive homonymous field defect were present. On two separate occasions colonmetry was performed and each time, after 200 cc of fluid had run in, there was a powerful contraction wave with leakage around the tube. Cystometry showed a similar degree of hyperirritability of the bladder (Fig 4).

Discussion—The cerebral cortex inhibits the spinal reflex activity of the bladder² and apparently of the colon as well. It thereby increases the storage capacity of these hollow viscera. Lesions situated in the cortex or brain stem frequently remove this inhibitory action and result in hypertonicity. Sensation usually remains unaltered.

II DESTRUCTION OF SPINAL CORD ABOVE SACRAL LEVEL

Case 3—Rita H, female, age 21. Spina bifida from twelfth thoracic to fourth lumbar vertebra, with infiltrating lipoma.

The patient had had spastic legs and absence of sensation below her eleventh thoracic segment since infancy. In 1933, Dr W J Mixer removed a mass of fatty tissue which compressed the lower end of her spinal cord from the twelfth thoracic to the fourth lumbar vertebra. Little improvement followed, and the patient had just managed to get about with the aid of leg braces and a pair of crutches, but had had the good fortune to have an adequately functioning automatic bladder.

Her colonmetrogram (Fig 5) shows an unusual hypertonicity of the colon with frequent peristaltic waves and fluctuating alterations of pressure from 40 to 90 cm. Fluoroscopic observation during a barium enema revealed an abnormally large colon with deep peristaltic waves which swept over its transverse and sigmoid loops. The barium was repeatedly forced down against the Foley bag and leaked around it when the balloon was not drawn tightly against the anal sphincter. The patient's only knowledge of filling was brought to her by the increasing spasticity of her legs. It is surprising that an individual with such an unusually hypertonic colon should be very constipated and only able to move her bowels with difficulty once a week.

Case 4—Stephen C, male, age 18. Epidural abscess in upper thoracic spine (T4 to T6), drained four weeks previously.

In this case an extradural collection of pus had compressed the spinal cord and resulted in a spastic paraplegia with very feeble movements in the left leg and paralysis of the right. Anesthesia was complete in his right lower leg, but some position and pain sensation remained on the left. Colonmetry revealed an increase of tone nearly as intense as that shown in Figure 5. His sensation of filling, which was not destroyed, was most peculiar. He never felt the usual suprapubic cramp-like discomfort, but at 300 cc noted discomfort in his penis and rectum and at 700 cc complained of fulness in his chest. Abnormal subjective localization of sensation is not unusual after incomplete spinal injuries and is often seen on distending the bladder, compression of the testicle, and even on cutaneous stimulation.

Discussion—Unfortunately, we have not yet been able to obtain a colon-metrogram immediately after a transverse injury to the spinal cord in its cervical or thoracic portions. During the stage of “spinal shock” there is a flaccid paralysis of the limbs with abolition of the tendon reflexes. It is also well established that there is a flaccid paralysis of the bladder, since cystometry shows practically no rise in tone or peristaltic contractions, even when a large amount of fluid is run in. During this stage of general reflex depression, patients have abdominal distention with no audible peristalsis, and usually fail to expel an enema or even gas through a rectal tube. Plain roentgenograms reveal large quantities of gas trapped in the small and large intestines. We have colon-metric and cystometric evidence in two patients, secured between two and three weeks after transverse spinal injuries, that the colon recovers its muscular tone more rapidly than the bladder, since in both of these patients the atonic stage persisted in the bladder, whereas the colon was already developing its chronic hypertonic state.

The remarkable hypertonia which soon develops after high injuries to the spinal cord is well shown in Figure 5. These physiologic changes in the spastic colon have not been adequately described previously, but they closely resemble the condition observed in the bladder by Munro¹ and McLellan² after satisfactory treatment and recovery of automatic bladder function. The abnormalities observed in this group of patients are not unlike those in the preceding group with intracranial lesions, except for the fact that patients with spinal injuries have little or no sensation. Both groups may have sudden and imperative necessity to defecate or urinate, or in spite of their hyperactive reflex tone may be definitely constipated, but the patients with spinal injury often do not know when they are soiling themselves.

III DESTRUCTION OF SACRAL CENTERS IN CORD OR CAUDA EQUINA

Case 5—Herbert M., male, age 43. Fracture of the twelfth thoracic vertebra one year previously, with compression and injury to cord.

A fall from a scaffolding had resulted in paraplegia, for which a decompressive laminectomy from the eleventh thoracic to the second lumbar vertebra had been performed at another hospital. Thereafter he had recovered to a remarkable degree, so that he could walk without support, although his legs remained somewhat weak and his tendon

Rita H. Spina Bifida with Myelitis at T11

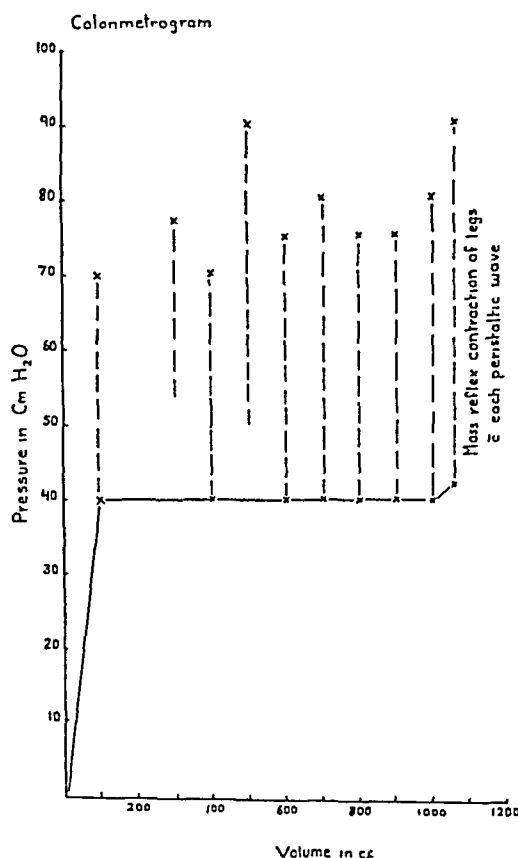


FIG 5—Case 3. The “reflex colon” with extreme hypertonia after a transverse spinal lesion at the eleventh thoracic segment.

reflexes nearly flaccid. He had regained sensation down to the fourth lumbar segment, but remained totally anesthetic over the sacral dermatomes. His bladder, which had been treated by prolonged catheter drainage, was rigid-walled and contracted to 100 cc maximum capacity. It was totally insensitive and dribbled constantly. His anal sphincter was also paralyzed, but he had not suffered from incontinence.

The colonmetrogram (Fig 6) shows the characteristic hypotonia and absence of peristaltic waves commonly seen in injury to the sacral centers of the spinal cord or more distal structures. Accurate sensation was gone, although he mentioned a peculiar feeling in his left testicle at a filling of 1,000 cc and a slight desire to defecate at 2,000 cc. At 2,800 cc he felt nauseated, but he had no pain or true sense of distention. In spite of these abnormalities the patient did not complain of any difficulty with his bowels.

Case 6—Emma H., female, age 43. Paralysis of lower sacral nerves after intrathecal alcohol injection.

Two intrathecal injections of 0.8 cc of absolute alcohol had been performed upon

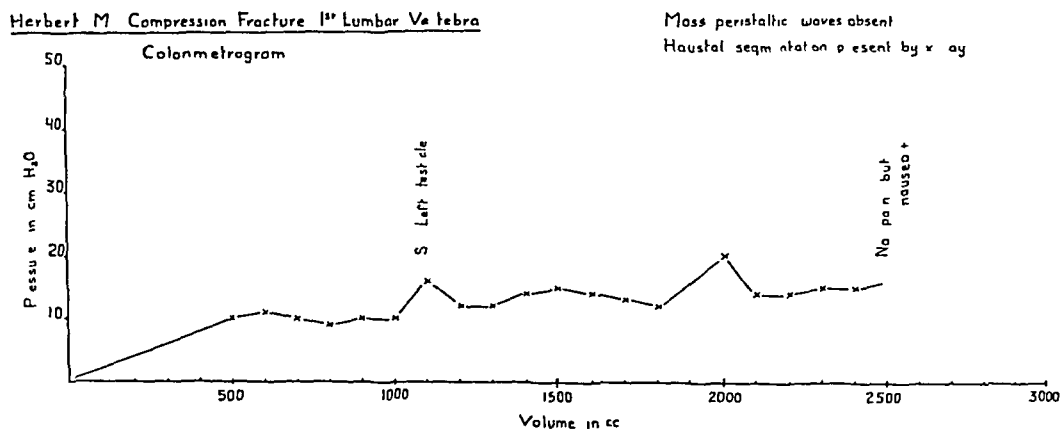


FIG 6—Case 5. The atonic colonmetrogram found after injury to the sacral segments of the spinal cord.

this patient six days apart, for the relief of a painful thigh amputation stump. After the second injection she complained of great difficulty in emptying her bladder, with absence of sensation on micturition or defecation. She developed a large urinary residual and had to be placed on tidal drainage. In addition, she noticed that it was difficult to move her bowels without an enema. On neurologic examination, abnormal findings were localized to the structures supplied by the second to fifth sacral nerves. They consisted of a narrow zone of anesthesia around the anus and forward over the perineum to the labia minora, and weakness of her sphincters.

Both her colon and cystometrograms disclosed a state of atonia and flaccid paralysis, with nearly complete loss of sensation (Fig 7). Peristaltic waves appeared in the colonmetrogram, and the patient noticed an aching sensation above her umbilicus only after distention to 1,700 cc. The bladder was more severely injured and showed no muscular response to stretching.

Discussion—Destruction of the cauda equina, or of the sacral segments in the spinal cord, produces a severe functional disturbance of the colon as well as the bladder, because the sacral pathways which transmit the contraction reflex are interrupted. Fluoroscopic observations show a loss of peristaltic rush waves, but haustral segmentation remains. Loss of sensation in the lower half of the colon is complete (Fig 7). It is theoretically possible that the cecum and ascending colon may retain some residual sensation, as this area is supposed to receive its innervation from the splanchnic trunks. Although the

sensation of a full rectum is abolished and the anal sphincter paralyzed the patient may notice few symptoms beyond mild constipation and soiling when he has diarrhea. Experimental megacolon has been produced in animals by Adamson and And⁶ by cutting the pelvic nerves, and it would seem as though such a condition were developing in Case 5.

Emma H. Paralysis Lower Sacral Nerves (from intrathecal alcohol injection)

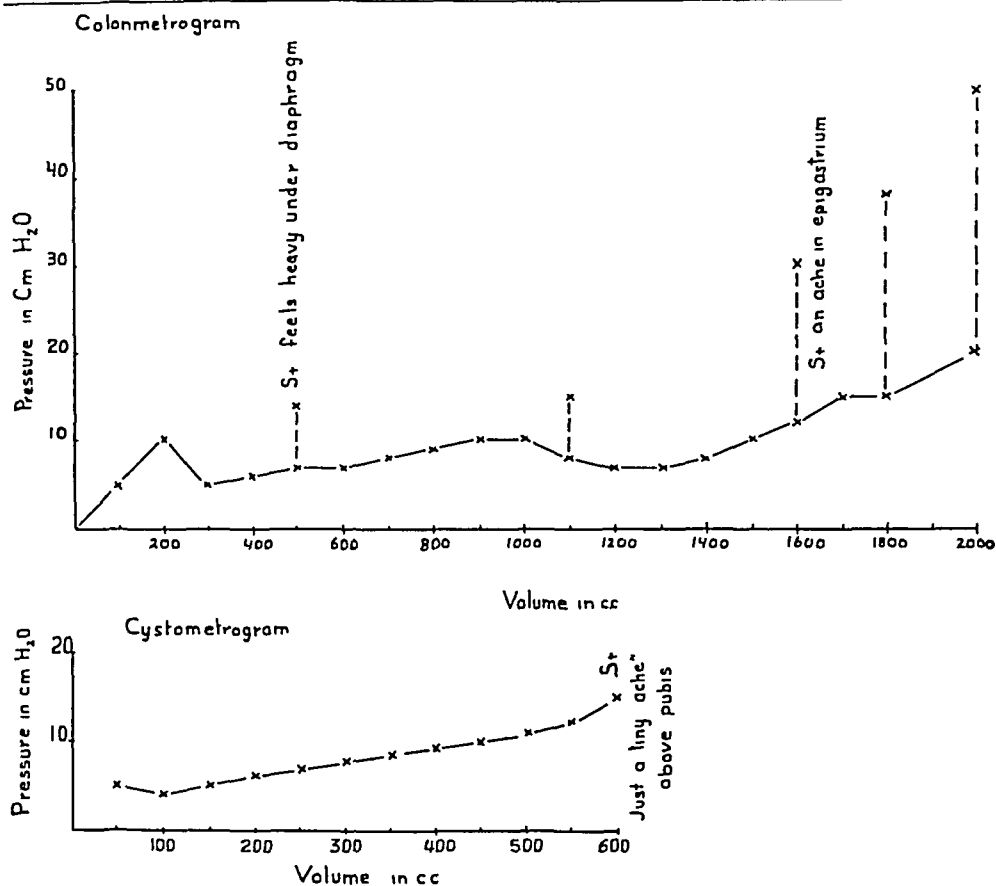


FIG 7—Case 6 Hypotonia of colon and atonia of bladder after chemical injury to lower sacral roots in cauda equina

IV DESTRUCTION OF LOWER SENSORY NERVE ROOTS AND POSTERIOR COLUMNS

A In Syphilis of Central Nervous System

A few months before this investigation was begun, a male, age 57, entered the hospital for treatment of long-standing neurosyphilis. He gave a history of increasing constipation and abdominal distention. These symptoms had followed a recent onset of numbness and ataxia in his legs. In a plain abdominal roentgenogram the right half of the colon and lower ileum were seen to be distended with gas. The cecum was huge. In addition, he had an enormously distended bladder. Both the blood Hinton and spinal fluid Wassermann tests were positive. His spinal fluid examination gave normal pressure and dynamics, two lymphocytes, a total protein of 67 mg, and gold sol 5555532100. In addition to the typical pupillary findings, ataxia, and loss of deep reflexes, he showed an unusual degree of muscular weakness in his legs with loss of pain and temperature sense. Because the reason for his distention was not recognized and it was felt that rupture of the cecum was imminent, a cecostomy was performed. The cecostomy tube failed to drain and the abdominal distention continued. Signs of bronchopneumonia set in and he died in four days. Autopsy revealed no peritonitis or organic obstruction, but

a thin-walled and enormously dilated colon, moderate distention of the small intestine, and a hypertrophic, chronically dilated bladder. Gross and microscopic examination of the brain and spinal cord established the diagnosis of meningovascular syphilis with recent patchy ischemic lesions of the spinal cord.

The patient died of paralytic ileus. The process involved his entire intestinal tract, but most particularly the cecum and ascending colon. From what we have learned through subsequent investigation the evidence clearly indicates that the acute intestinal paralysis was caused by a syphilitic vascular process with acute degeneration of the sensory and reflex mechanism which mediate defecation.

Colonmetry has since been carried out in three other patients with neurosyphilitic disturbances of defecation.

Case 7—Frank C., male, age 72. Taboparesis with megacolon.

This patient, the first to be studied by colonmetry, entered the hospital in December, 1938. He was a Cape Verde Island Negro, with much mental deterioration, and an

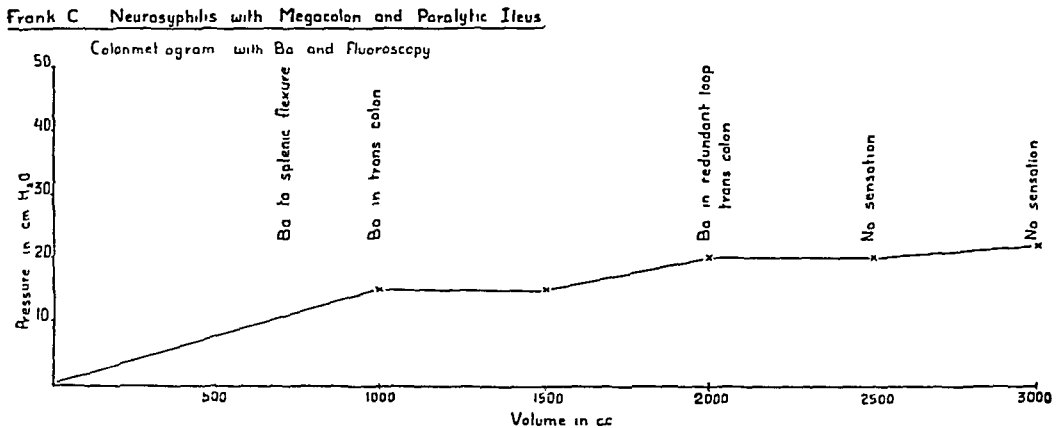


FIG 8—Case 7. Extreme atonia and megacolon which may occur in neurosyphilis with involvement of posterior root fibers in sacral cord.

enormously distended abdomen. He said that the illness had begun four months before with pain in the abdomen and increasing constipation. Although vomiting was denied, peristalsis was visible and audible. His pupils were unequal and did not react to light. Position sense in his hands and feet was practically nonexistent and his gait moderately ataxic. His knee jerks were much reduced and ankle jerks absent. Examination of the cerebrospinal fluid was characteristic of general paresis, *i.e.*, protein 45 mg, eight cells (lymphocytes), Wassermann positive, and gold sol 555532110.

Operation for intestinal obstruction was considered, but Dr. G. W. Holmes, who examined the plain roentgenograms, made the diagnosis of megacolon and felt that this could be on a luetic basis. Therapy consisted in colonic irrigations which removed an enormous quantity of fecal material and reduced distention.

A colonmetrogram was performed, using a dilute barium mixture and combining fluoroscopic observation with determination of intracolonic pressure (Fig. 8). At the time of this test his colon was already distended with a large amount of barium which he had been unable to expel after a previous fluoroscopic examination, yet he was able to hold an additional 3,000 cc without any sense of distention or evidence of peristaltic contractions. A cystometrogram, made a few days later, did not show a similar degree of bladder atonia, although the patient noticed no sensation until over 500 cc of liquid had been introduced.

Colon- and cystometrograms were made upon two other patients with latent neurosyphilis. Both had positive spinal fluid findings, but failed to show characteristic neurologic signs of the disease. The first case was of interest

from a general surgical viewpoint because constipation and straining at stool had caused a recurrence of his bilateral inguinal herniae after careful repair carried out with fascia lata. Although his cystometrogram was normal, a colonmetrogram disclosed a large bowel of abnormal capacity (3,000 cc) with low basic tone, absent peristalsis, and markedly diminished sensation. He was able to move his bowels only with extreme difficulty every three to five days and it was felt that this was the cause of his recurrent herniae. The second patient was tested routinely while he was in the hospital for investigation of a urinary residual of from 120 to 400 cc. Cystometry showed a typical tabetic bladder with very poor tone and greatly reduced sensation. His colon had an equally low basic tone and feeble peristalsis, although its sensation was within the normal range.

B In "Combined System Disease" of Spinal Cord

Case 8—John D., male, age 69. Pernicious anemia with spastic-ataxic legs and retention of urine from subacute degeneration of posterior and lateral columns of spinal cord.

Unsteadiness in gait had forced the patient to use a cane for three years. Sixteen months before admission he had lost all position-sense in his legs and the ability to walk at all. Difficulty in urination had been present for a week and progressed to complete retention in the last 24 hours; constipation had been troublesome for many years. Blood examination showed R B C 2,500,000. Hemoglobin 55 per cent. Color index 1.1. Gastric acidity was absent in fasting stomach contents and after histamine. Neurologic examination showed extreme ataxia and spasticity. He had sufficient strength in his legs to stand, but no sensation below the knees and an absence of position and vibration sense from the waist down. In addition his legs were extremely spastic. Figure 9 shows an atonic dilation with absence of peristalsis and abnormal sensation in both the colon and bladder.

Discussion—In both tabes dorsalis and combined system disease of the spinal cord there is injury to the posterior columns of Goll and Burdach,⁷ and in tabes to the sensory root fibers as well. In the tabetic, the spinal stretch reflexes are abolished and reflex contractility of the bladder and colon may be lost. In combined system disease, where there is usually degeneration of both the pyramidal and dorsal tracts, the legs may become spastic. As we have seen, spasticity alone is usually accompanied by hypertonia of the colon and bladder, but whenever there is extensive damage to the posterior roots which carry sensation from the colon and bladder, or of the reflex arc at any point, an atonic dilatation will result. The so-called "tabetic bladder" has long been recognized as a dreaded complication of syphilis of the spinal cord, and a similar condition in severe primary anemias and cachexias is well known. But it is not common knowledge that the degenerative process may also destroy the detrusor mechanism of the colon. We wish particularly, to bring this to the attention of surgeons, so that it may be recognized that these conditions can produce megacolon, simulate intestinal obstruction, and cause a breaking down of herniae which have been adequately repaired.

In addition to the typical neurogenic disturbances of defecation described above, we have obtained colonmetric evidence of dilatation of the colon with

severe degrees of hypotonia in psychotic depressed patients and others after prolonged constipation from neglect. A flaccid dilatation of the colon has often been observed during fluoroscopic examinations in this group of patients

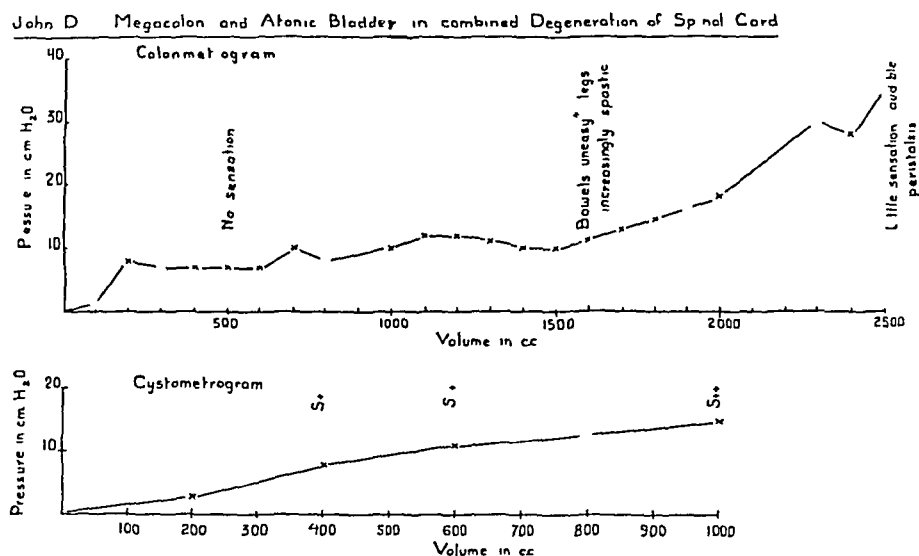


FIG. 9.—Case 8. Flaccid paralysis of colon and bladder with dilatation seen in a patient with combined system disease.

by Dr. J. R. Lingley,⁸ who has made a special study of this problem. The condition may be classified as “acquired megacolon” and is not due primarily to lesions of the descending pathways or of the spinal reflex arc.

TABLE I

NEUROGENIC DISTURBANCES OF THE COLON

Case No.	Pathologic Lesion	Uninhibited Colon	Reflex Colon	Autonomous Colon	Atonic Colon	Peristaltic Waves	Sensation	Colon Capacity
1	Parasellar cyst epidermoid	+				Increased	Normal	Greatly decreased
2	Left frontotemporal glioma	+				Increased	?	Greatly decreased
3	Spina bifida with transverse myelitis to T ₁₁		+			Increased	0	Increased
4	Epidural abscess with incomplete destruction of cord T ₄ -T ₆		+			Increased	Present but abnormal	Slightly decreased
5	Compression fracture of T ₁ vertebra with recovery down to lower lumbar segments			+		Absent	0	Greatly increased
6	Chemical destruction of sacral nerves			+		Reduced	Much reduced	Normal
7	Taboparesis with paralytic ileus				+	Absent	0	Megacolon
8	Combined degeneration of spinal cord				+	Absent	0	Greatly increased

General Discussion—Injuries to the brain, spinal cord, and sacral parasympathetic nerves may be followed by serious disturbances in defecation. Similar neurogenic disturbances in vesical function have been recognized for years and referred to, both ungrammatically and unphysiologically, as “cord-

bladder" Through the physiologic investigations of Elliott,⁹ and the more recent neurologic and clinical studies of Denny-Brown and Robertson,¹⁰ Langworthy and Kolb,¹¹ Munro⁵ and McLellan,² it has been established that the bladder reacts reflexly to distention and stretching of its walls. Since this response of smooth muscle is mediated by a reflex arc through the spinal cord it is affected by a neurologic lesion in a manner quite analogous to that observed in skeletal muscle. It is the purpose of this communication to show that a similar mechanism governs the activity of the colon and that injury to its cortical centers, descending pathways, or reflex arcs can be fitted into an exact neurologic classification. By observing the reaction of the colon to distention, we can determine whether its muscular tone is normal, increased, decreased, or absent, whether the upper or lower motor neuron is functioning abnormally, and whether the lesion involves the sensory or the motor portion of the reflex arc.

Disease or injury of the brain and descending tracts of spinal cord removes cerebral control over the reflex peristaltic contractions which sweep the fecal contents down the colon and pack it into the rectum. In the baby, and in some adult idiots, cerebral voluntary control of micturition and defecation is not developed. Urine and feces are ejected at irregular intervals in response to a stretch reflex. With the gradual development of cortical function, a cerebral control is established over these spinal reflexes. Its elimination results in increased reflex contractions in the smooth muscle which lines the hollow viscera. Injury to the brain or to the tracts in the spinal cord produces an identical increase in the tone of the colon and bladder. After the initial flaccid paralysis has been replaced by the permanent spastic state, a reversion to the infantile condition is common, with precipitate evacuation of urine and, to a lesser extent, feces. In spinal lesions sensation is lost in addition to cortical control. The resulting disturbances are shown in Figures 3 to 5.

Elliott⁹ found that destruction of the spinal cord at progressively lower levels did not destroy reflex evacuation of the bladder until the second, third, and fourth sacral segments were removed. Destruction of these segments, which give rise to the parasympathetic motor as well as the sensory fibers to the bladder, abolishes reflex activity. This also appears to be the case with the colon in man. It would seem, furthermore, that the sacral nerves constitute the only motor and sensory pathway to the colon. We have made colonometric studies upon two patients before and after extensive lumbar ganglionectomies, and on two others with bilateral lumbar ganglionectomy plus splanchnicectomy, and have been unable to detect any significant change either in the motor response to filling or in sensation.* Figures 6 and 7 illustrate the reduction in tone and peristaltic contractions which, together with a loss of the normal sensation of distention, characterizes destruction of the spinal reflex arc, *i e*, cells in the sacral segments of the cord or of their axones.

* The conclusion that the thoracolumbar sympathetic rami carry no important sensorimotor fibers to the bladder has already been reached by Munro⁵ and McLellan.²

in the cauda equina and pelvic nerves. Lesions of this sort cause a much greater disturbance in the excretory processes than those which affect the tracts and brain.

An even greater disturbance of the bladder and colon results from destruction of the afferent fibers in the posterior sacral roots or in the sacral portion of the spinal cord. The bladder disturbances in *tubes dorsalis* and combined system diseases have been commonly recognized, but this has not been the case with the colon. Disturbances of the nervous mechanism that evacuates the colon may be very severe and lead to fatal ileus or simulate intestinal obstruction. Because the paralysis of the colon is of the flaccid type, colostomy is more likely to do harm than good. These patients may also develop striking degrees of megacolon (Fig 8), but there is no reason to suppose that the dilated, atonic bowel can be improved by sympathectomy. The only logical way to handle these conditions is by early, adequate treatment. The filling curves of the bladder and colon should be determined when the patient with neurosyphilis or pernicious anemia first complains of sensory disturbances, because medical treatment of these diseases can prevent their neurologic complications far more effectively than it can correct them in their advanced stages.

A final point, which we wish to emphasize, is that the neurogenic mechanism is not necessarily upset to the same degree in both bladder and colon. For example, the filling curves in Case 6 (Fig 7) illustrate a distinctly greater loss of tone and reflex activity in the bladder than in the colon. On the other hand, in Case 7, and in the next patient with neurosyphilis described above, there was much less paralysis and sensory loss in the bladder than in the colon. While the reflex arcs to the bladder and colon follow a closely similar course, it is evident that they are not exactly similar.

CLASSIFICATION OF NEUROGENIC DISTURBANCES OF THE COLON

Munro⁵ has proposed a valuable classification of bladder disturbances which result from neurologic lesions. This has been expanded in McLellan's² recent monograph on the "neurogenic bladder." The same classification can be applied with equal satisfaction to neurogenic disturbances of the colon, and is reproduced, herewith, in the form given by McLellan with necessary minor adaptations to the colon. This classification should be compared with the data given in Table I.

GROUP I THE UNINHIBITED COLON (FIGS 3 AND 4)

Resulting from lack or loss of cerebral inhibition, either from failure of development, cortical disease, or subtotal destruction of the spinal cord pathways—defecation is imperative, but voluntary. Sensory pathways are intact.

GROUP II THE REFLEX COLON (FIG 5)

Resulting from widespread injury of the controlling mechanisms from disease or injury of the brain (sensory as well as motor cortex or brain stem),

or from destruction of the cord (above the sacral segments)—defecation is purely reflex, but often less imperative or precipitate than the evacuation of urine. Sensation is abolished.

GROUP III THE AUTONOMOUS COLON (FIGS 6 AND 7)

Resulting from nuclear or infanuclear lesions of the sacral cord, cauda equina, or sacral plexus with interruption of both afferent and efferent fibers of the spinal reflex arc. Only segmental peristalsis (haustrial markings) remains and is presumably mediated by the intrinsic plexuses of Meissner and Auerbach. Emptying of the colon is impaired, but less so than the bladder. Mild degrees of megacolon may result. Sensation is abolished.

GROUP IV THE ATONIC COLON (FIGS 8 AND 9)

Resulting from lesions of the pelvic parasympathetic nerves, or posterior sacral roots and columns with interruption of the afferent fibers of the reflex arc. There is a profound disturbance of normal voluntary and reflex evacuation, which may be as severe in the colon as in the bladder. Extreme degrees of megacolon may result. Sensation is abolished.

SUMMARY AND CONCLUSIONS

(1) The colonmetrogram is the filling curve obtained by slowly distending the large intestine with warm water. The resultant graph, in which the intracolonic pressure is plotted against the volume of liquid introduced, closely resembles the cystometrogram. A normal colon can accommodate itself to a volume roughly four times greater than the bladder.

(2) Colonmetry gives a picture of the motor activity and sensation of the colon as a whole. It fails to bring out circumscribed disturbances in the rectum, sigmoid, or upper portions of the large bowel. This is not a serious objection in nerve lesions, because neurogenic disturbances characteristically affect the entire length of the colon.

(3) The longitudinal and circular smooth muscle of the large intestine reacts to increased filling by periodic attempts to evacuate. This is illustrated in the colonmetrogram by intermittent rises in pressure and in the fluoroscopic examination by peristaltic rush waves which sweep the fecal contents down into the rectum.

(4) The peristaltic contractions are a form of "stretch-reflex." The afferent and efferent arcs of this spinal reflex run over the parasympathetic sacral ramus, the second, third and fourth sacral roots in the cauda equina, and the corresponding segments in the lower end of the spinal cord.

(5) The normal patient becomes aware of a sensation of filling in his colon or bladder at a pressure between 20 and 30 cm. of water. At 40 to 50 cm. there is a real urge to defecate or urinate and at higher pressures distinct low abdominal pain.

(6) Lesions to the brain, spinal cord, and sacral nerves produce characteristic disturbances in the physiologic mechanism of evacuation which are

common to both colon and bladder. These are analogous to alterations in the knee jerk and other tendon jerks, which are dependent upon the stretch-reflex of skeletal muscle.

(7) The colonmetrogram shows a hypertonic response to filling with lesions of the motor fibers in the brain or in the descending spinal tracts (spastic paralysis), and an atonic bowel when the lesion is situated in the sacral segments of the cord, cauda equina, or pelvic plexuses (flaccid paralysis). In addition, much depends on the degree of sensory loss, the severest grades of paralysis being found in patients with degenerative disease of the sensory fibers in the sacral cord.

(8) These changes are illustrated by a series of colonmetrograms obtained from patients with lesions at various levels of the nervous system.

(9) It is shown that the same neurologic classification that has been adopted for injuries of bladder innervation can be applied to the colon. The colonmetrogram, like the cystometrogram, is a valuable aid for differential diagnosis of the level of the nervous system which is destroyed by injury or disease.

(10) Neurologic disturbances of defecation, which are of importance to the general surgeon, can best be evaluated by colonmetry. These comprise cases of acute ileus seen after injury to the spinal cord and in rarer instances of spinal neurosyphilis. A variety of megacolon, as well as of atonic paralysis of the bladder, is not uncommon in patients with neurosyphilis or combined system disease. These patients are forced to strain so hard to move their bowels that herniae may be produced. In addition, the patient with spastic or flaccid paraplegia often complains of difficulty in evacuating his bowels as well as his bladder.

We wish to express our thanks to the members of the Roentgenologic Department of the Massachusetts General Hospital for their assistance in studying pressure-volume reactions of the colon by direct fluoroscopic observations in the course of colonmetry.

REFERENCES

- ¹ Rose, D. K. Determination of Bladder Pressure with the Cystometer. *J. A. M. A.*, **88**, 151-157, 1927.
- ² McLellan, F. C. *The Neurogenic Bladder*. Charles C. Thomas, Springfield, Ill., 206, 1939.
- ³ Joltrain, E., Baufle, P., and Coope, R. Essai de mesure de la pression du gros intestin. *Bull. et Mem. Soc. Med. Hop. de Paris*, **43**, 211-213, 1919.
- ⁴ Denny-Brown, D., and Robertson, C. Graeme. An Investigation of the Nervous Control of Defecation. *Brain*, **58**, 256-310, 1935.
- ⁵ Munro, D. The Cord Bladder. *Jour. Urol.*, **36**, 710-729, 1936.
- ⁶ Adamson, W. A. D., and Aird, I. Megacolon. Evidence in Favour of a Neurogenic Origin. *Brit. Jour. Surg.*, **20**, 220-233, 1932.
- ⁷ Wechsler, I. S. *A Textbook of Clinical Neurology*. W. B. Saunders Co., Philadelphia, 3rd ed., 759, 1933.
- ⁸ Linglev, J. R. Personal communication.
- ⁹ Elliott, T. R. The Innervation of the Bladder and Urethra. *Jour. Physiol.*, **35**, 367-445, 1907.

- ¹⁰ Denny-Brown, D., and Robertson, E. Graeme On the Physiology of Micturition
Brain, 56, 149-190, 1933
- ¹¹ Langworthy, O. R., and Kolb, L. C. The Encephalic Control of Tone in the Musculature of the Ordinary Bladder Brain, 56, 371-382, 1933

DISCUSSION —DR PETER HEINBECKER (St. Louis, Mo.) I wish to express our gratitude to Doctor White for this presentation in which he has depicted for us the development of colonmetrography. I feel that this method, especially when combined with anesthesia at the proper level, should help us to decide whether or not interference with the sympathetic nerve supply would do good in many cases of functional disturbance of the bowel.

DR JAMES C. WHITE (Boston, Mass., closing) I might take just one moment to say that I think the next stage in this work is going to be to see what happens after different operative lesions. I know that after a satisfactory cordotomy the bladder sensation is little changed and the bladder reflexes are preserved. We have been interested in doing colonmetriograms as well as cystometriograms after injury to the sympathetic pathways alone. We have found that the colonmetrogram in a patient after bilateral lumbar ganglionectomy for Raynaud's disease or in a patient in whom the upper lumbar ganglia as well as both splanchnic nerves have been removed for hypertension, shows no change in the motor responses of the colon or bladder. We have not been able to detect any sensory changes either. All of these tests have been made upon normal colons, and it looks as though all sensation, as well as all motor control, must come over these second, third, and fourth pairs of sacral parasympathetic rami. That is the conclusion reached by Munro, McLellan, and Denny-Brown and Robertson, who did such careful work on the bladder, and by the last two investigators for the rectal innervation as well. We wonder what happens in children with Hirschsprung's disease, who we know react so well to removal of the sympathetic nerve supply. To date, no opportunity has presented itself to test the motor and sensory responses in a case of megacolon before and after sympathectomy.

THE EARLY SYMPTOMS AND TREATMENT OF NASOPHARYNGEAL TUMORS*

LOYAL DAVIS, M D

AND

JOHN MARTIN, M D

CHICAGO, ILL

FROM THE DIVISION OF SURGERY, NORTHWESTERN UNIVERSITY MEDICAL SCHOOL, CHICAGO, ILL., AND THE CUSHING TUMOR
REGISTRY, NEW HAVEN, CONN.

IT IS NOT an uncommon experience for the neurologic surgeon to be consulted by a patient who has suddenly developed unilateral paralysis of the extra-ocular muscles, pain or numbness in the areas of distribution of the trigeminal nerve, and even signs of destruction of the cranial nerves which lie in the posterior cranial fossa, with little or no evidence of an increase in intracranial pressure.

Such symptoms should suggest several possible intracranial lesions, not the least of which is an extension of a malignant tumor of the nasopharynx, accessory nasal sinuses, or middle ear cavity. We have recently had occasion to study the histories of 15 such patients with malignant neoplasms of the upper respiratory tract. Nine of these cases were from the files of the Cushing Tumor Registry, and the other six patients were referred to us for neurologic consultation and treatment. We have been so impressed by the uniformity of both the early and late symptoms in these patients, as well as by the fact that they frequently have not had an adequate early examination of their pharynx, nose, and ears, and have not had a complete history recorded, that we believe that a restatement of the early symptoms is particularly important.

Gordon New,¹ in 1922, emphasized the fact that the effects of the regional metastases of nasopharyngeal malignancies, such as facial pain and diplopia, and not the effects of the primary lesion, may bring the patient to the physician. It was his plea, then, that the *early* symptoms of such tumors be recognized for their full value. It is true that the signs of metastases may develop rapidly, but in the 15 cases which we have studied this never occurred in the absence of unmistakable signs of the primary tumor, which should have been provocative of a careful examination, if not an actual diagnosis.

A patient with a malignant tumor of the nasopharynx which is still a local growth may complain of a stuffiness or feeling of fullness in the nose, and frequently there is a thin, watery nasal discharge, or even mucopus. Slight or massive spontaneous nasal hemorrhages occur from time to time. Anosmia and fetor may be present. A fullness in the ear, perhaps with tinnitus, will be relieved only temporarily by eustachian insufflation. There may be a complaint of moderate earache, with pain radiating down the wall of the pharynx.

* Presented by title before the American Surgical Association, St. Louis, Mo., May 1, 2, 3, 1940.

into the neck. Deafness may cause the patient to seek an examination of his ears, and one or both drums will be found to be dull, sclerotic, and retracted. Not infrequently a seropurulent discharge appears suddenly from the middle ear and drains persistently from an opening in the drum. Very frequently there is unilateral cervical adenopathy and occasionally it is bilateral. The patient may complain of a feeling of thickness in the region of the soft palate, swallowing becomes difficult, and the speech becomes nasal in quality. Almost always there is either a localized headache or pain in the trigeminal area of the face, sometimes the patient locates the pain only vaguely, deep within the face.

Any patient with such a train of symptoms obviously deserves a thorough examination by someone competent to recognize even a small lesion which may lie in the pharyngeal or nasal cavities. Nasal polypoid masses are not always "simple polypi", a "hyperplastic" nasal, or pharyngeal mucous membrane requires more than casual observations, nasal discharge or epistaxis never occurs without good cause, "thickening" of "nodules" in the vault of the pharynx may not be "lymphoid hyperplasia", sinus membranes may be more than "cystically degenerated" or "chronically thickened", and facial pain can be caused by disease other than infected teeth or tonsils. In short, a painstaking examination of the ears, sinuses, nasal passages, and nasopharynx must be accomplished, and it is a rare patient indeed who cannot be so examined, either by direct view with a nasopharyngoscope or indirectly with a mirror. Any mass, thus discovered, should be biopsied and the patient held under observation until a diagnosis has been made. It must be emphasized, also, that the biopsy should not be too superficial, for some carcinomata of the nasopharynx may, especially in their early stages, be submucosal, and a shallow biopsy will reveal only lymphoid infiltration. Roentgenographic evidence of an early malignancy in the epipharynx, nose, or ear is usually lacking.

If a malignant tumor is discovered, deep roentgenotherapy or radium treatment may be begun at once, and while the growth is still local the prognosis is not too unfavorable. Examination having failed to disclose a growth, or, as is more often the case, no examination having been made, the patient next appears with unmistakable signs of intracranial spread, and the eventual outlook is then generally unfavorable. A unilateral primary lesion often presents early only unilateral symptoms, but the signs of intracranial extension are frequently bilateral or even contralateral. The spreading tumor, extending along the floor of the cranium, may or may not produce blindness, but such blindness is due to direct pressure and invasion of the optic nerve, and is not the result of postedema atrophy. The third, fourth, and sixth nerves are usually involved early in the spread of the growing mass so that diplopia of increasing severity becomes a source of great concern to the patient. Complete ptosis and ophthalmoplegia are common in the later stages. Pain in the area of supply of any one or all, of the branches of the trigeminal nerve frequently appears and a full blown Gradenigo syndrome may develop, which, with a discharging ear, will sometimes be the source of confusion in diagnosis. The

facial pain is usually not paroxysmal but is frequently felt as a deep-seated, poorly localized distress, and not uncommonly an area of hypesthesia or actual sensory loss will be found on examination. The occasional patient develops a complete facial paralysis, and tinnitus or vertigo is a usual and early sign of intracranial spread to the posterior cranial fossa. Deafness was complete in three of our cases. Palatal weakness with the resultant changes in speech and deglutition, together with nausea and vomiting, speaks for an expansion of the tumor along the brain stem. Again, roentgenograms, more frequently than not, will show no bony changes, and, indeed, at this time they are hardly needed, for with such positive evidence of the location of a spreading tumor, the diagnosis becomes self-evident. The gross appearance of the mass in the nasopharynx at this late stage is so characteristic that biopsy becomes merely a confirmatory procedure.



FIG 1

" FIG 2

FIG 3

FIG 1—Case 1. One week after operation. Showing the complete ptosis of the left upper lid which had been present for six weeks.

FIG 2—The same patient looking to the right, showing the ophthalmoplegia on the left.

FIG 3—The same patient looking to the left. There was no motion in the left eye upon looking in any direction. The pupil was fixed in moderate dilatation, and the eye was completely blind.

Two typical cases which have been under our direct observation and care are reviewed briefly.

Case 1—L. K., white, male, age 45, had suffered from a left-sided headache for seven weeks, localized vaguely behind the left eye, and for five weeks had noted a progressive ptosis and dimming of vision of the left eye. Upon his first admission to the hospital there was a complete left ptosis, left ophthalmoplegia, loss of all vision in the left eye, dilation and fixation of the left pupil, and loss of sensation to pain and light touch over the left cheek (Figs. 1, 2, and 3). He had had a "stuffy" left nostril for some time without any other sign of respiratory infection. He had lost 15 pounds in weight. There was no loss of smell, hearing, taste, or the ability to move either side of the face, to swallow, or to speak normally. Casual examination of the nose and throat revealed nothing, but upon careful inspection of the superior meatus on the left a gray, firm, cartilage-like mass was seen, obscuring all view of the ethmoid area. It was painless and bled but little on being touched. Roentgenograms revealed a beginning erosion of the floor of the left middle cranial fossa. A subtemporal exploratory operation, under local anesthesia, brought into view a tumor mass lying anteriorly, under the wing of the sphenoid bone, deep within the middle cranial fossa. Tissue from this tumor and from

that of the nose revealed a myxoid type of sarcoma with frequent islands of cartilage and few mitotic figures (Figs 4 and 5)

The patient had several attacks of nosebleed while in the hospital but he made a prompt recovery from his operation. Deep roentgenotherapy was started at once following which he felt somewhat improved, but though there was some improvement in the ptosis on the left, there was progressive loss of vision in the right eye, so that he was totally blind in both eyes two months after he was first seen. At no time was there any papilledema. Four months after his operation, he was admitted through the emergency ward following a massive and uncontrollable nasal hemorrhage. The nasal tumor had become a huge, ulcerated mass, completely filling the left side of the nose and nasopharynx. There was at that time a complete recovery of the left ptosis, and perfectly normal movement of the right eyeball was still present. There was no cervical

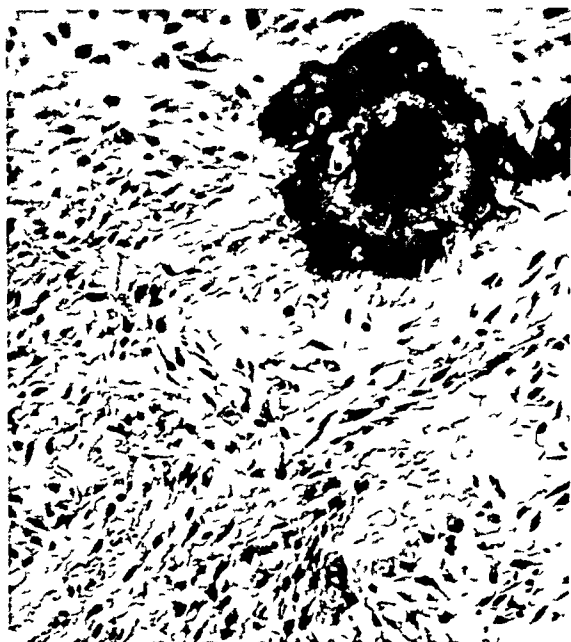


FIG 4

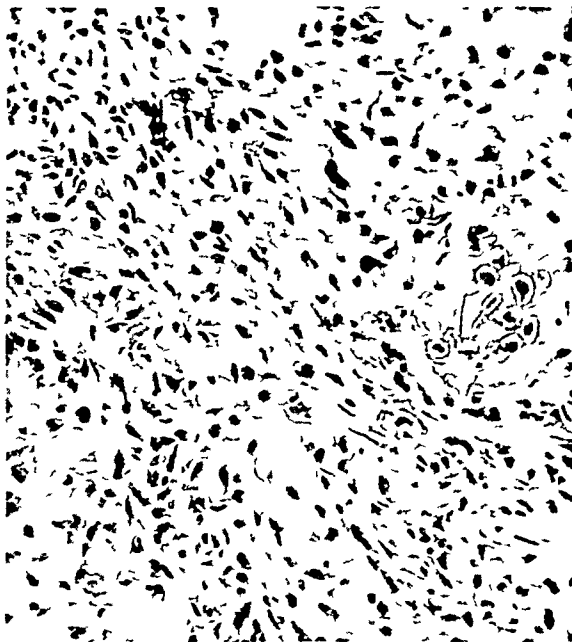


FIG 5

FIG 4—Case 1. This photomicrograph ($\times 130$) is from tissue removed for biopsy from the nose, and it shows discrete islands of both adult and embryonic cartilage. The main mass of tissue is made up of large stellate or spindle shaped cells which are not closely packed and which lie in a moderately vascular, somewhat vasculotized, collagenous, intercellular groundwork. Mitoses are not particularly abundant. There is a large element of fibrocytes. *Pathologic Diagnosis:* Spindle cell myxosarcoma with cartilage formation, of low malignancy.

FIG 5—Case 1. This photomicrograph ($\times 130$) is from tissue removed at operation from the middle cranial fossa, and it answers the same approximate description as does that of Figure 4. There is no adult cartilage in this intracranial tumor, however, and the young cartilage, which is quite abundant and makes up approximately one fifth of the tumor, is a much more prominent feature than it is in the primary or nasal lesion.

adenopathy. In his terminal stage, his intracranial symptoms consisted of bilateral complete blindness, paralysis of the left third, fourth, and sixth nerves, loss of sensation in the area of supply of the left maxillary nerve, and severe generalized headache. He failed rapidly and died five days after his second admission. Permission for autopsy was refused.

COMMENT—This patient illustrates the fact that prodromal nasopharyngeal symptoms may be quite meager and precede for a short time only, the signs of intracranial extension. However, had this man had a thorough examination of his nose when he first began to complain of headache, nasal blockage, and drooping of the left lid, the tumor no doubt could have been identified. The intracranial mass must have remained localized to the middle

fossa, probably extending backward from the original tumor through the posterior ethmoid and sphenoid area, and though the mass was demonstrated at operation to be of a considerable size, fundus examination at no time during the four-month period showed any swelling of the optic disks. It is doubtful if any form of either surgical or radiation therapy could have controlled this tumor.

A more encouraging outcome resulted in another patient who gave a typical history and clinical findings of a nasopharyngeal tumor with intracranial extension.

Case 2—R. C., white, male, age 39, was admitted for neurologic study because of a diminution of hearing and a sensation that the left ear was plugged shut for five and one-half weeks, right-sided periorbital pain for five weeks, diplopia on looking to the right for three weeks, numbness of the skin under the right eye for two weeks, and difficulty in swallowing for two weeks. He had had a nasal discharge of mucus for several weeks. He was found to have a widened left palpebral fissure, a complete right rectus paralysis, nystagmus on looking to the left, anesthesia of the right maxillary area, diminution of the right corneal reflex, deafness in the left ear, a paralysis of the left side of the soft palate, and a voice of nasal quality. There was no complaint of headache. The pupillary reflexes were intact, there were no changes in the retinæ, no papilledema, and no loss in the visual fields. Examination of the ears revealed bilaterally sclerotic tympanic membranes with an old perforation on the right. In the vault of the nasopharynx, obstructing the orifice of the left eustachian tube, was a mulberry-like mass of nodular tissue the size of a large olive, and extending from it across the roof and to the right side of the nasopharynx was an apron-like sheet of the same tissue. Large vessels were seen in the mass. A biopsy of the tumor, which was made with great caution because of its vascularity, was returned with the diagnosis of "dense lymphoid infiltration with chronic inflammation." Because of the gross appearance of the lesion so typical of carcinoma, and because of the undeniable signs of intracranial extension, the patient was immediately started upon a course of radium treatment. For the next six months he received, as an ambulatory patient, 4,000 mg hrs of radium over the left nasopharyngeal area, 4,000 mg hrs over the right nasopharyngeal area, 248,000 mg hrs over the right temporal area, and 46,000 mg hrs anteriorly over the nose, all in the form of external packs. Three and one-half months after the beginning of this treatment, only a small pea-sized nubbin of sclerotic tumor tissue remained in the vault just to the left of the midline, and most of his neurologic symptoms had disappeared. Now, three years following his last treatment, he is in perfect health, has not a single vestige of his former intracranial complications, and the mucosa of his epipharynx is smooth, thin, and moderately atrophic.

COMMENT—This man undoubtedly had a visible nasopharyngeal tumor before he developed an intracranial extension, for the complaints of deafness, nasal discharge, and a feeling of fullness in the left ear were logical ones, considering the site of the main tumor mass. The case illustrates the fact that the most striking neurologic sign, in this case paralysis of the right lateral rectus, may be contralateral to the primary lesion, but that, as in Case 1, the intracranial symptoms eventually become bilateral. We are positive, from the gross appearance of the tumor, the intracranial symptoms, and the response to radium treatment, that this tumor was a carcinoma, and we are more than ever impressed that a biopsy, to be of any value at all, must be deep and furnish an adequate amount of tissue. It is quite conceivable that a lymphoid reaction had occurred over the surface of this tumor, and from this

example it is apparent that when this is true this superficial layer of tissue must be passed through before the actual tumor tissue can be reached. We consider this case a complete cure to date, and would compare it to a similar case reported by Saignon and his associates.²

This paper is not intended to be a histopathologic discussion, but mention should be made of the types of tumors in this series of the probable method of their extension into the cranial cavity, and of the confusion of pathologic terms used in the description of malignancies of the upper respiratory tract. The patients in our series varied in age from 13 to 78 years. Eleven were males,



FIG 6

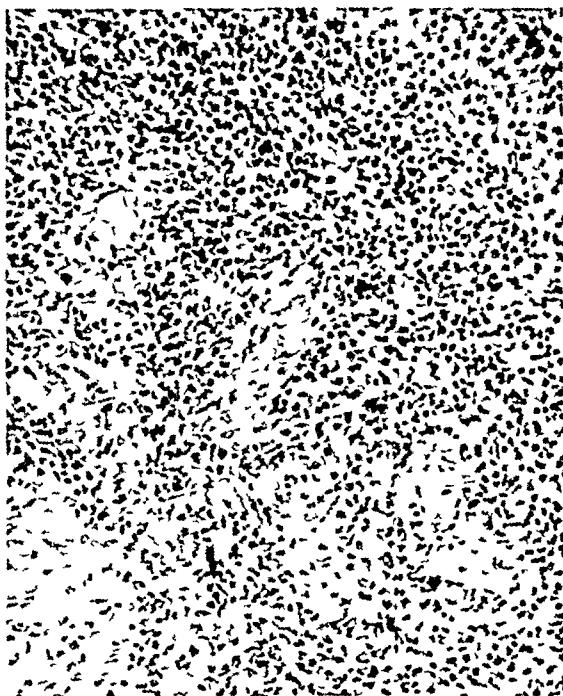


FIG 7

FIG 6—Case S. C. Because of severe and intractable pain in the entire area of distribution of the right trigeminal nerve due to a carcinoma of the right maxillary sinus, a section of the posterior root of the trigeminal nerve was undertaken. This photomicrograph (X130) is from an intra-cranial extension of the antral tumor, the secondary tumor mass filling the inner portion of the right middle cranial fossa. The tissue was white, soft, and gelatinous in consistency when it was removed from the area of the gasserian ganglion. It is composed of small, gland-like structures resembling acini or alveoli. Occasionally these formations are solid but usually their walls are but two or three cell layers thick and they are filled with a colloidal-like substance which stains poorly. The cells are flattened and cuboidal, contain a darkly staining nucleus and scant cytoplasm, and show only an occasional mitotic figure. *Pathologic Diagnosis: Adenocarcinoma.*

FIG 7—Case W. H. This photomicrograph (X175) is taken from biopsy material from a nasopharyngeal tumor in a patient who had advanced signs of intracranial extension. There are fairly discrete masses of large, oval, squamous-like cells, with pale centrally placed nuclei and light staining cytoplasm. Many of these cells show mitotic figures. There is no keratinization. There is a marked lymphocytic infiltration, with some fibrocytes. This type of tumor is therefore, frequently called lymphocarcinoma. We prefer the simpler term squamous cell carcinoma.

and four females. In 12 patients the tumors were carcinomata, two were sarcomata, and one was a "lymphoma." The primary tumor was in the nasopharynx in seven cases, ear, two cases, nose, three cases, sinuses, three cases (two antrum, one ethmoid). Every case showed far advanced signs of intracranial spread and several of the patients experienced their first otolaryngologic examination only after coming under neurologic observation.¹

The method of extension of these tumors has been believed to be by one of three pathways: (1) By the lymphatics, (2) by the blood vessels (veins),

and (3) by direct tissue extension. Certainly lymphatic metastasis can and does occur into the cervical lymph nodes, but the most likely and most demonstrable pathway of intracranial spread is that of direct invasion. The many foramina at the base of the skull, the patent eustachian tubes, the thin-walled sinuses (sphenoid, ethmoid), and the occasional persistent Rathke pouch, all invite direct extension of a malignant, expanding mass in their close vicinity. Certainly, the orderly progression of intracranial symptoms indicates a spread of the tumor in this manner, and besides, there are no intracranial lymphatics.

The matter of terminology has reached a stage of such an admixture of names for these tumors that one author scarcely knows what another means



FIG 8—Case I P. A biopsy of this tumor mass from the fossa of Rosenmüller revealed a vascular tumor of mixed cell type. Large clear squamous like cells occur in collections and are also mixed throughout the remainder of the tissue which is made up of lymphocytes and dense fibrous areas where the cells are almost all adult fibrocytes. There is no keratin formation. Mitoses are fairly common and may be seen in this photomicrograph ($\times 175$). The tumor is of uneven structure some areas being of low cellularity others densely packed. The patient died of an intracranial extension of the tumor. *Pathologic Diagnosis* Squamous cell carcinoma.

when a tumor is classified according to some special type. At present "lymphoid" tumors are called lympho-endothelioma, lymphoma, lymphoblastoma, lymphosarcoma, and lymphocarcinoma. Sarcomata are classified as round cell, spindle cell, giant cell melanomyxo-, chondro-, and fibrosarcoma, according to their predominating microscopic characteristic. Carcinomata lead the list for variety probably because they are the most common tumor of a malignant nature to be found in the nose and nasopharynx. They are called squamous cell, basal cell, transitional cell, anaplastic, keratinizing nonkeratinizing, scirrhous, adenomatous, or cylindromatous, with little regard for a histogenetic classification on the embryologic cell type. Hauser and Brownell³ believe they show "that all epithelial neoplasms arising from the membranes of the nasopharynx are medullary, squa-

mous cell carcinomata, and that it is not necessary to employ such terms as lympho-epithelioma and transitional cell carcinoma." Furstenberg⁴ agrees that the commonest lesion is the squamous cell carcinoma. Salinger and Pearlman,⁵ in an extensive histopathologic study, would classify nasopharyngeal malignant tumors as carcinoma, sarcoma, and endothelioma. They, too, recognize the confusion in present day terminology, but they feel justified in using the terms "anaplastic" and "transitional cell" carcinoma.

In any event, squamous cell carcinomata are apparently the most frequent malignant tumors of the epipharynx, nose, and middle ear (Figs 6, 7, and 8)

In the pharynx, they are slow-growing, firm, sessile, vascular, and appear either as a local, elevated nodule or as a thinner, more sheet-like mass which may cover several square centimeters of the vault. In the nose, they may appear to be hard, rubbery, and not at all vascular, or they may appear to be a soft, irregular ulcerated mass which bleeds on the slightest provocation. In one elderly patient the nasal carcinoma was a pale, flat, watery mass which resembled very closely a sessile polyp. Carcinomata of the middle ear cavity, evaginating through a rupture in the tympanic membrane, may, at first, be mistaken for a polyp, and in one of our cases several such "polypi" were removed in succession until it occurred to the examiner that a biopsy might explain the reason for their regrowth. It did, the "polypi" were carcinoma.

When a primary lesion of the nose, ear, or pharynx is not seen or suspected, but the patient is suffering from progressive symptoms of some sort of basilar cranial lesion, the problem becomes first of all one of differential diagnosis. Paratrigeminal lesions, most commonly meningiomata or aneurysms, such as have recently been described by us,⁶ will come first to mind, and the signs of intracranial involvement may be so localized to the middle fossa as to lead to operation. Chordomata, basilar meningiomata, acoustic neuromata, and aneurysms must be excluded until the primary tumor has been discovered, but in most cases their exclusion will not be a difficult task.

We believe, after a study of this group of cases, and of some of those reported elsewhere, that it is the responsibility of every physician treating diseases of the ear, nose, and throat to be alert to the possible presence of malignant tumors in his field of examination—to look with suspicion upon the patient who complains of vague or incomplete symptoms of the upper respiratory tract, that it is usually evidence of carelessness on some examiner's part at some time during the patient's history, if the patient arrives in the hands of the neurologic surgeon with signs of intracranial extension from a nasopharyngeal tumor which is only then seen for the first time. It is not denied that such lesions present a challenge to accurate early diagnosis, but it is apparently true that frequently the early diagnostic studies are inadequate and desultory.

One cannot review this subject and emerge completely optimistic over the general prognosis yet we would not agree with Fuistenberg⁴ that "treatment is exceedingly futile and the prognosis hopelessly discouraging." An early diagnosis with the early institution of radium or deep roentgenotherapy, the histologic characteristics of the tumor having been established, seems to offer the best source of a hope for control of the tumor. It is doubtful if surgery ever accomplishes very much in the treatment of a nasopharyngeal malignancy, the location and tendency to direct intracranial spread preclude the effectiveness of any type of operation which has so far been attempted.

REFERENCES

- ¹ New, Gordon. Syndrome of Malignant Tumors of the Nasopharynx. J A M A, 79, 10-14, July 1, 1922

- ² Saignon, Ponthius, and Perion Epithelioma peritubaire, etc Lyon Med, 162, 99-103, 1938
- ³ Hauser, I J, and Brownell, D H Malignant Neoplasms of the Nasopharynx J A M A, 111, 2467-2473, December 31, 1938
- ⁴ Furstenberg, A C Malignant Neoplasms of the Nasopharynx Surg, Gynec and Obstet, 66, 400-404, 1938
- ⁵ Salinger, S, and Peailman, S J Malignant Tumors of the Epipharynx Trans Amer Acad Ophth and Otolaryng, 280-316, 1935
- ⁶ Davis, L and Martin, J Surgical Lesions of the Paratrigeminal Area J A M A, 113, 1952-1955 November 25, 1939

TRANSTHORACIC BRONCHOTOMY FOR REMOVAL OF BENIGN TUMORS OF THE BRONCHI^{*}

LEO ELOESSER, M D

SAN FRANCISCO, CALIF

FROM THE STANFORD SURGICAL SERVICE AT THE SAN FRANCISCO HOSPITAL DEPARTMENT OF PUBLIC HEALTH,
SAN FRANCISCO CALIF

BRONCHOTOMY, in its narrower sense of incision into a bronchus, apparently dates from 1900, when Gluck proposed the operation for low tracheal stenosis, it had the object of permitting retrograde respiration through a large bronchial fistula. The operation seems to have been discussed and written about more than it was actually carried out. Sauerbruch mentions having performed it once, most other texts on thoracic surgery fail to mention it. The bronchotomies of older authors, from Bonetus down, reviewed by Gross in his treatise on foreign bodies in the air passages, include operative openings into the larynx and trachea, but not the bronchi. The lower bronchi, however, have been entered, *via* a posterior mediastinal route, with the object of extracting foreign bodies. Schwartz, in Quénu's Clinic, worked out such a procedure which was carried out successfully by Duncan, Schiasso, *et al*. Danielson mentions three transpleural bronchotomies. The establishment of a large bronchial fistula may, occasionally, be indicated for incurable low tracheal stenosis, modern bronchoscopic methods have superseded bronchotomy for removal of foreign bodies.

Formal bronchotomy may have a place, however, in the treatment of benign bronchial tumors. Bigger,¹ in 1935, reported an operation performed upon a boy for a tumor of the left main bronchus. The bronchus was incised and the tumor removed, one week later the chest was reopened and the left lung removed. The course was complicated by a purulent pericarditis, to which the patient succumbed. Many pedunculated benign tumors, especially adenomata, may be removed bronchoscopically, they may be avulsed with a forceps or snare and their pedicles may be coagulated or cauterized. Some tumors, however, cannot be treated satisfactorily by endoscopic methods, especially those with pedicles originating in the upper lobe bronchus and sessile tumors with a broad base. Such tumors may be reached, and the possibility of their removal more accurately estimated through an incision into the bronchus than through a bronchoscope. Bronchotomy may even be justifiable for some more accessible bronchial growths. For it is notoriously difficult to judge whether a tumor mass seen protruding into the mouth of a bronchoscopic tube actually represents the whole tumor or merely the top of a submerged mass, of which, like a floating iceberg, but a small portion is visible while the great bulk lies submerged.

^{*} Presented by title before the American Surgical Association, St. Louis, Mo., May 1, 2, 3, 1940.

Bronchotomy *via* a thoracotomy opening allows accurate inspection of a growth, of its base and its extension, if palpation of the affected lobe discloses a large induration, of which it may be assumed that but a small portion has protruded into the bronchial lumen, while the main tumor lies or has extended extrabronchially, lobectomy or pneumonectomy may be undertaken at once. Otherwise the bronchus may be opened between stay sutures, the growth may be removed, its base cauterized and a portion of the bronchial wall removed with it, if necessary. The incision into the bronchus may then be repaired by suture and the chest closed, with or without drainage as seems most expedient. A long posterior thoracotomy incision with resection of the fifth rib, as described by Crafoord² for pneumonectomy, gives good access. The lung is retracted forward. The hilum is injected subpleurally with 15–20 cc of 1/2 per cent procaine, to which epinephrine (two drops to 30 cc) has been added. The procaine injection stops the objectionable cough reflex that follows handling of the hilar structures, and the edema resulting from the injection makes their dissection peculiarly easy. The hilar pleura is incised, the bronchial wall is steadied by two fine silk stay sutures passed through its soft posterior membranous portion and incised at a site calculated by bronchoscopic and roentgenographic observation. The lumen is inspected, the incision prolonged if necessary and the tumor removed. The incision is repaired with a single layer of fine catgut or silk sutures including the whole thickness of the bronchial wall, care being taken to narrow the bronchial lumen as little as possible. More than one layer would be likely to lead to a stenosis. Repair of the intrapulmonary portion of the bronchus, where lung may be used to cover the suture line, is easier than that of the hilar portion. The suture need not be hermetically accurate, in the case reported it was far from so, yet the incision closed without sequela.

It would seem best in patients who cough not to attempt to cover the bronchial sutures by reuniting the incision into the hilar pleura. If the bronchus does leak air it is better that an escape into the pleura than into the mediastinum, mediastinal emphysema being a complication more difficult to handle than a pneumothorax, which is easily taken care of by a drainage tube.

The thoracotomy incision is closed, if the bronchial suture seems tight, drainage may be dispensed with, although the patient should be carefully watched for the first few days after operation and a pressure pneumothorax promptly dealt with. If there is doubt of an air leak a catheter is introduced into the chest through a separate intercostal stab and led out under water.

Through the kindness of Dr. Cabot Brown, I was afforded the opportunity of carrying out a bronchotomy for what was thought, preoperatively, to be a benign tumor.

Case Report—Mrs. Elise Y., age 33, was referred by Doctor Brown to the Stanford Surgical Service at the San Francisco Hospital, June 19, 1939. She had suffered for five years from chronic, intermittent obstruction of the left upper lobe, with febrile interludes, abscess formation, much cough and episodes of bleeding. A series of roentgenograms, dating from 1934 to 1937, showed intermittent obstruction of the left upper lobe. Lipiodol

injection by Doctor Brown, in April, 1939, demonstrated a round defect projecting into the bronchial lumen, at this site an obstruction was encountered bronchoscopically (Fig 1) An abscess was drained through an interior incision in April, 1939 Bronchoscopy, four times repeated, failed to reveal a tumor and biopsies revealed nothing but shreds of inflamed bronchial mucosa A ureteral catheter, introduced into the draining sinus of the previous thoracotomy, passed into the lower lobe bronchus beyond the site of obstruction, and a second catheter, introduced through the bronchoscope, traversed the stricture and also passed into the lower bronchus, but no ulcerative lesion, and no tumor mass, from which a biopsy could be taken, were seen However, suspicion of a growth could not be allayed and exploratory bronchotomy was decided upon



FIG 1—Bronchogram with lipiodol April 26 1939
Filling defect shown just above the bifurcation of the left
stem bronchus

Operation—October 2, 1939 Under completely satisfactory anesthesia with avertin and gas, administered by Doctor Neff through an intratracheal tube, the chest was opened by Claford's incision, 22 cm of the fifth rib was resected Separation of dense adhesions offered considerable difficulty, those over the upper lobe were allowed to remain The left lower bronchus was identified and opened between two stay sutures by a transverse incision into its membranous posterior portion, a catheter introduced into it and passed upwards met with no resistance Upon close inspection one saw that the bronchus had been opened exactly opposite a tumor, which was attached by a pedicle to a site near the mouth of the upper lobe bronchus As it hung down by its pedicle it occluded the upper lobe bronchus entirely and the lower lobe bronchus partially Its anatomic situation explained its not having been visible through the bronchoscope, for coughing during the introduction of the bronchoscope had probably pushed it back into the upper lobe bronchus, where it remained hidden

The incision was carried around at an angle so as to open the left upper bronchus, the tumor, measuring 1.5 x 1.4 x 1.2 cm was carefully lifted up and removed by severing its pedicle with the diathermy current The pedicle was inspected, its base cauterized again, and the incision closed with a series of fine, interrupted, chromic gut sutures

placed in one layer. The thoracotomy incision was closed, but a Pezzer catheter was placed in its posterior angle, the closure of the bronchus having seemed none too accurate.

Pathologic Diagnosis—Dr David Wood: Carcinoma, relatively benign.

Postoperative Course—The catheter was submerged under water. On the second day, a small amount of subcutaneous emphysema was demonstrable over the sternal notch, a venous pressure of 21 cm gave additional evidence of mediastinal emphysema. This, however, rapidly receded and the subsequent course was uneventful. The patient was discharged, November 2, 1939. There has been no evidence of recurrence. The left upper lobe is aerated.



FIG 2—Lipiodol injection 29 days after operation, October 31, 1939. Both upper and lower lobe bronchi are open. (The central density is due to previous lipiodol injections into the abscess cavity.)

Lipiodol injection, October 31, 1939, demonstrated both upper and lower left bronchi to be open (Fig 2). Bronchoscopy several months later revealed a normal bronchial tree.

CONCLUSION

Transpleural bronchotomy is a feasible, conservative method of removing benign tumors of the bronchus, which, by reason of their anatomic situation or their doubtful extension, are not amenable to safe and certain bronchoscopic removal.

REFERENCES

- ¹ Bigger, I. A. Diagnosis and Treatment of Primary Carcinoma of Lung. *So Surg*, 4, 401, December, 1935.
- ² Crafoord, C. Technique of Pneumonectomy in Man. *Acta Chir Scandinav*, 81, Sup 54, 11, May, 1938.

THE REPAIR OF INGUINAL HERNIA WITH TRANSPLANTATION OF THE CORD TO THE FEMORAL CANAL*

A PRELIMINARY REPORT

WILLIAM F. MACFEE, M.D.

NEW YORK, N. Y.

FROM THE DEPARTMENT OF SURGERY OF THE NEW YORK HOSPITAL AND CORNELL MEDICAL COLLEGE, AND THE SURGICAL SERVICES OF ST. LUKE'S HOSPITAL, NEW YORK, N. Y.

ATTEMPTS to improve the results of operations for hernia have progressed in three general directions. First, the tissues available for repair have been utilized in a number of different ways, second, many kinds of suture material have been employed, and third, various dispositions of the spermatic cord have been made. The necessity of providing room for exit of the cord has always been an obstacle to satisfactory repair. Wherever it may be placed the cord interferes to some extent with closure of the hernial defect and leaves a possible pathway for recurrence.

Bassini¹ met this problem by transferring the cord to a new position, between the internal and external oblique muscles. Halsted,^{2, 3} in his earlier operations, placed it exterior to the aponeurosis of the external oblique muscle. In ten of a series of herniae in children, reported in 1895, Coley⁴ allowed the cord to remain in its normal location and, in 1899, Feigerson⁵ advised against altering its position in the treatment of herniae in adults. In his later operations Halsted⁶ also left the cord in its natural site.

In order to reduce the size of the cord Halsted³ at one time recommended the division of part of the spermatic veins at the point of exit. This feature of the operation was later abandoned. With the same idea in mind Torek⁷ separated the elements of the cord at the internal ring and brought them out at different levels in the line of repair, the size of the opening necessary for the cord was thereby reduced. In certain cases Quain,⁸ Skillern⁹ and Eidman¹⁰ have excised or divided the cremaster. Buidick¹¹ and his associates, in selected types of hernia, have completely divided the cord and so eliminated it as an obstacle to repair. Castration has sometimes been resorted to in older men but this procedure is not usually accepted with enthusiasm.

Cheever¹² conceived the idea of transplanting the cord to the femoral canal and, in 1923, during a discussion of certain papers^{13, 14, 15} on hernia which had been presented before the American Surgical Association he called attention to the operation as follows:

"Dr. Seelig's beautiful demonstration of the futility of suturing the muscle fibers to Poupart's ligament, and Dr. Gallie's very convincing demonstration of one way to avoid it, make it reasonable, perhaps, to propose a somewhat novel method of curing inguinal hernia. Underlying all these new procedures is the widespread recognition that old methods are by no means always suc-

* Read before the American Surgical Association, St. Louis, Mo., May 3, 1940.

cessful This new method consists in withdrawing the testicle from the scrotum, incising the transversalis fascia forming the floor of the inguinal canal and slipping the testicle down through the femoral canal beneath the ligament and between the vein and Gimbernat's ligament out through the saphenous opening and back into the scrotum This will sound fanciful to you, but it is apparently perfectly practicable, and I have carried it out in five cases with apparent success" So far as I have been able to determine, Cheever is the first to have conceived and carried out this plan of disposition of the cord

The possibility of utilizing the femoral canal as path of exit for the cord first suggested itself to me through the reading of an article by Fauntleroy¹⁶ in which he described a patient whose spermatic cord was found as a congenital anomaly in the femoral canal Apparently, the testis had followed the femoral route in its descent to the scrotum The practicability of transferring the cord to the femoral canal was satisfactorily demonstrated on the cadaver, and I planned to try it in a suitable clinical case Upon asking the late Dr F S Mathews what he thought of such an operation I learned for the first time of Doctor Cheever's work Encouraged by Doctor Cheever's experience with the operation, I performed, between 1929 and 1933, six operations for recurrent or large primary herniae in elderly patients, completely freeing the testicle from its scrotal attachments in each instance and then reinserting it through the femoral canal into the scrotum The operation appeared to offer promise, but its performance presented certain technical difficulties In freeing the testicle from the scrotum numerous small blood vessels are encountered A second hindrance is the disproportion between the size of the testicle and the femoral canal through which it must pass, the canal in the male is usually small

It was obvious that these difficulties could be overcome by opening the femoral canal, it would then be possible to transfer the cord without disturbing the testicle, and repair of the inguinal ligament did not appear to offer any great difficulties With these considerations in mind the following plan of procedure was adopted

Operative Technique—The hernial sac is exposed through the usual incision, removed in the usual manner, and the defect in the transversalis muscle is closed (Fig 1) The inferior as well as the superior surfaces of the inguinal (Poupart's) and lacunar (Gimbernat's) ligaments are dissected free of fat and fascia, exposing the inferior outlet of the femoral canal and the fascial sheath of the pectineus muscle near its origin (Fig 2) The inguinal ligament is then detached by making an oblique incision along the sulcus which is formed by the inguinal aponeurotic falx (conjoined tendon) and the inguinal ligament where they are jointly attached to the pubic bone The detachment is completed by freeing the lacunar (Gimbernat's) ligament along the line of its pubic insertion and the cord is placed in the femoral canal (Figs 1 and 3)

The ligamentous structures are then brought over the cord and restored

to their normal relationships by means of a series of silk sutures (Figs 4 and 5) The sutures uniting the inguinal ligament to the pubic tubercle are preferably of the mattress type Those employed to restore the attachment to the superior pubic ramus may be simple interrupted sutures These are passed through the ligament of the pubes (Cooper's ligament) and tied, the ends being left long (Fig 5) The ligament which bears Cooper's¹⁷ name was described by him as a remarkably strong ligamentous expansion extending from the tuberosity of the pubes outwards, and projecting from the bone over the iliopectineal line The closure about the cord as it lies in the femoral canal is made snugly, and the technic is similar to the repair of a femoral hernia through the inguinal approach

The next step in the operation is the approximation of the internal oblique muscle to the pubic (Cooper's) ligament instead of Poupart's Gouard¹⁸ has adopted this plan in inguinal hernioplasty because he considers Cooper's ligament the stronger of the two The approximation is accomplished by using the long ends of the same sutures that were employed to reattach the inguino-lacunar ligament to the pubic bone (Fig 6) Additional sutures are placed anterior and lateral to the femoral canal to approximate the internal oblique muscle to the inguinal ligament We thus have the conjoined tendon and the medial portion of the internal oblique anchored to Cooper's ligament and the lateral portion of the internal oblique anchored to Poupart's The sutures are tied and obliteration of the inguinal defect is complete (Fig 7) The segment of cord lying between the internal inguinal ring and the femoral ring is buried and disappears from view

The opening in the aponeurosis of the external oblique muscle is closed by imbrication, the upper leaf being brought down over the lower (Figs 7 and 8) The sutures near the pubic tubercle may be made to include the cut end of the inguinal ligament and the integument of the bone in order to further reinforce the attachment of the ligament Medial to the transplanted cord, the margin of the upper leaf is brought down and sutured to the pectineal fascia, and lateral to the cord it is sutured to the fascia lata (Fig 8) The wound is then closed in the usual manner Care should be taken to see that the testis is well down in the scrotum before the patient leaves the operating room

The operation just described appears to be very similar to the procedure employed by Lisitsyn¹⁹ which has recently come to my attention In two cases reported in 1934, Lisitsyn, a Russian surgeon, divided the inguinal ligament near the pubic bone and opened the femoral canal The cord was then placed in the canal and the ligament rejoined by suture The aponeurosis of the external oblique muscle with the underlying tissues was sutured to the inguinal ligament and to the periosteum of the pubic bone He then transplanted a free piece of fascia lata over the repair for reinforcement of the suture line Lisitsyn's first operation of this kind was performed, April 3, 1929, for a recurrent hernia, and he reported that there had been no recurrence five years after operation

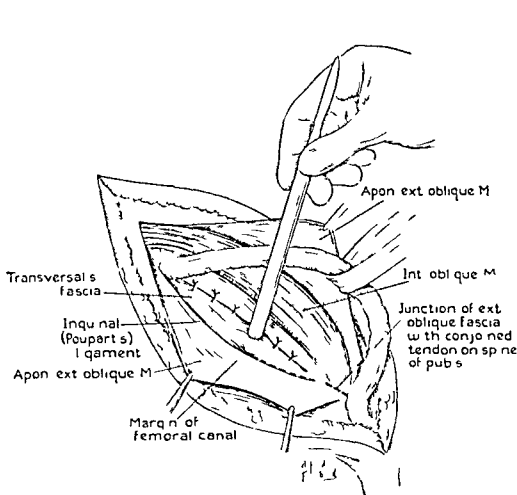


FIG 1

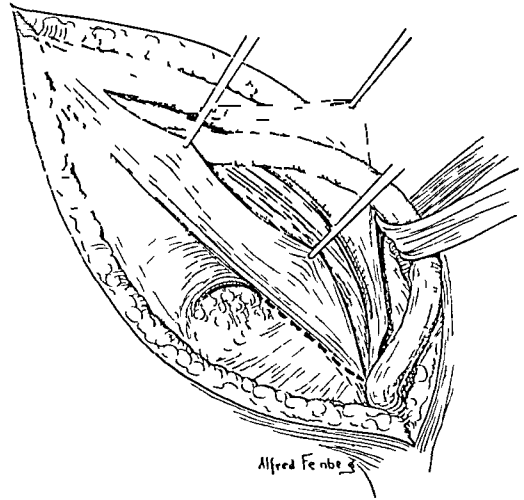


FIG 2

FIG 1—The hernial sac has been removed and the defect in the transversalis fascia sutured. The anterior margin of the femoral canal has been exposed and the incision designed to free the inguinal (Poupart's) ligament and open the femoral canal is indicated by the dotted line. The incision is started along the junction of the aponeurotic falx (conjoined tendon) and inguinal ligament on the pubic tubercle and carried laterally separating the ligament from its attachment to the superior pubic ramus, until the femoral canal is entered.

FIG 2—The inferior surface of the inguinal ligament has been cleared of fat and the fascial sheath of the pectineus muscle and the inferior aspect of the femoral canal are exposed. The dotted line shows the course of the incision which is to free the inguinal ligament, as seen from below.

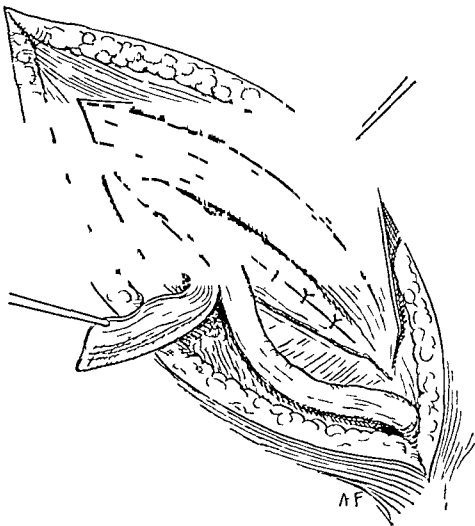


FIG 3

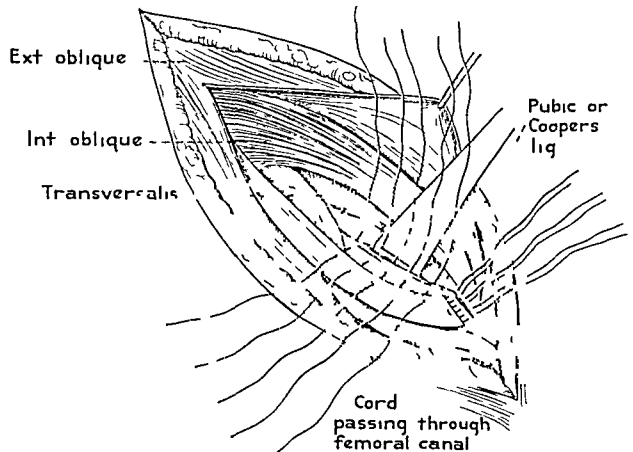


FIG 4

FIG 3—The inguinal ligament has been detached and the cord placed in the femoral canal.

FIG 4—Sutures have been placed to restore the ligament to its normal relationships. The anterior or medial three sutures are of the mattress type and rejoin the ligament to the pubic tubercle. The lateral sutures are of the simple interrupted type and are designed to approximate the shelving border of the inguinal ligament to the pubic (Cooper's) ligament.

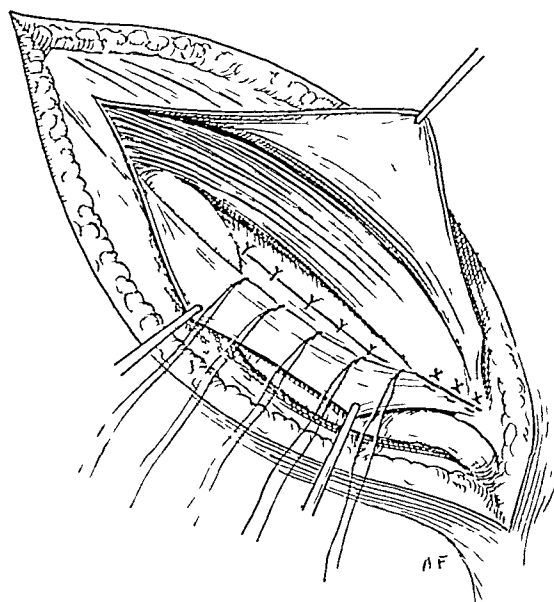


FIG 5

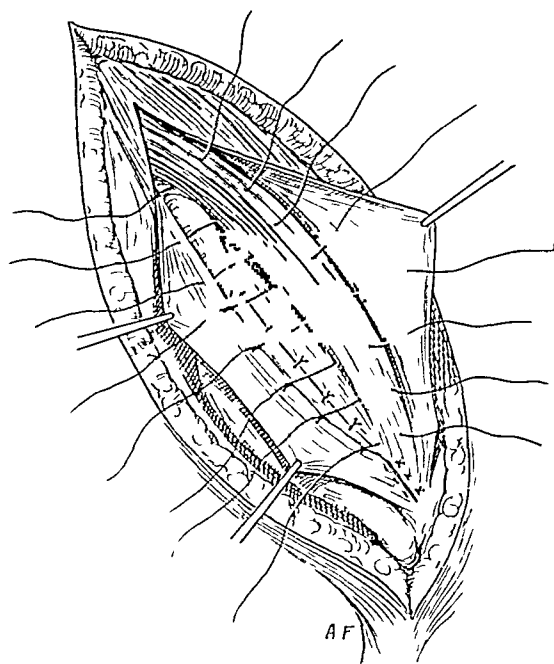


FIG 6

FIG 5—The sutures shown in Figure 4 have been tied, restoring the inguinal ligament and closing the femoral ring snugly about the cord. The ends of the lateral sutures have been left long so that they may be used to approximate the conjoint tendon and the internal oblique muscle to the pubic (Cooper's) ligament.

FIG 6—The long ends of the sutures shown in Figure 5 have been passed through the lower margin of the conjoint tendon and the internal oblique muscle. Additional sutures have been placed farther laterally to bring the internal oblique to the inguinal ligament.

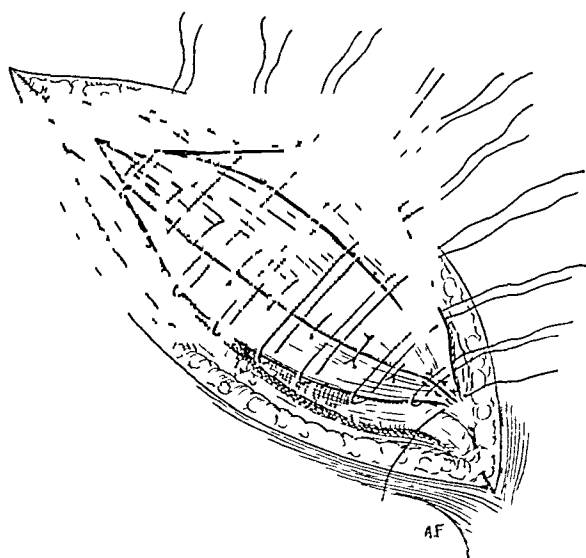


FIG 7

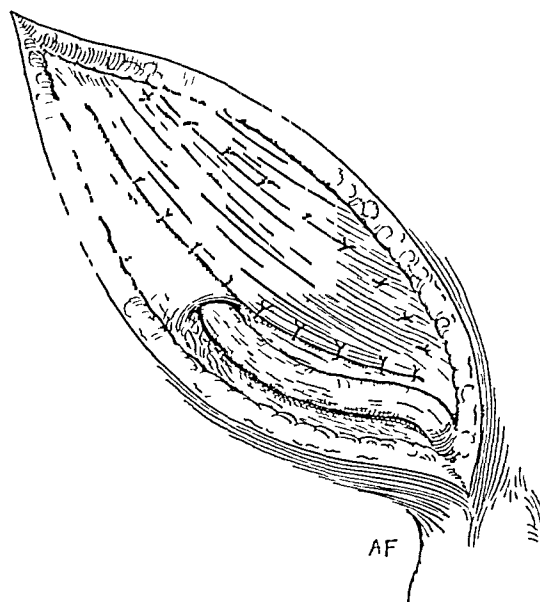


FIG 8

FIG 7—The conjoint tendon and the internal oblique muscle have been approximated to the pubic ligament medially and to the inguinal ligament laterally. The hernial defect is completely closed. Imbricating sutures have been placed in the aponeurosis of the external oblique.

FIG 8—The imbricating sutures have been tied and the margin of the upper leaf has been sutured medially to the fascial sheath of the pectineus muscle and laterally to the fascia lata of the thigh.

TABLE I
REPAIR OF PRIMARY AND RECURRENT INGUINAL HERNIAE WITH TRANSPLANTATION OF CORD TO THE FEMORAL CANAL, 33 CASES

History No	Age	Type of Hernia	Previous Repairs	Concurrent Diseases	Date of Operation	Operative Accidents	Postoperative Complications	Later Complications	Result
122-742	39	Recurrent lt indirect, sliding—en- tire sigmoid	Two	None	6/24/37	Division of spermatic artery	None	Atrophy of testicle	4/10/40—well
123-653	67	Recurrent lt indirect— incarcerated omentum	One	Chronic bron- chitis	8/31/37	None	Exacerbation of bronchitis-cough	None	4/6/40—well
124-073	63	Primary rt indirect, scrotal		Diabetes Arteriosclerosis Chronic myo- carditis	9/29/37	None	None	None	10/25/38— well 11/29/39— Died sud- denly No recurrence of hernia 4/7/40—well
148638	61	Primary rt direct		Obesity Arteriosclerosis Urinary incon- tinence	10/ 5/37	None	None	None	
156798	51	Primary rt direct		None	10/14/37	None	None	None	4/7/40—well
209321	50	Recurrent lt indirect Primary lt femoral	One	Chronic bron- chitis	7/23/38	None	Cough	None	4/7/40—fem- oral recur- rence
209321	50	Recurrent rt indirect	One	Chronic bron- chitis	8/ 4/38	None	Cough	None	4/7/40—well
210770	63	Primary rt direct		Prostatic hyper- trophy	8/13/38	None	None	None	4/21/40—well
129-530	51	Primary rt direct		None	8/17/38	None	None	None	4/24/40—well
129-680	49	Recurrent rt direct	One	None	8/23/38	None	None	None	4/12/40—well
210770	63	Primary lt direct		Prostatic hyper- trophy	8/30/38	None	None	None	4/21/40—well

REPAIR OF INGUINAL HERNIA

81047	48	Recurrent lt direct	Four	Syphilis	10/18/38	Division of spermatic artery	Edema of testicle	Atrophy of testicle	4/7/40—well
218169	56	Primary rt direct		Obesity	11/ 5/38	None	None	None	4/14/40—well
218977	51	Primary rt direct		Chronic bron- chitis	11/ 8/38	None	None	None	6/18/39—in- ginal recur- rence
218169	56	Primary lt direct		Obesity	11/19/38	None	Wound infection— <i>Staph aureus</i>	Delayed healing	4/14/40—in- ginal recur- rence
218977	51	Primary lt direct		Chronic bron- chitis	11/21/38	None	None	None	6/18/39—in- ginal recur- rence
A-10382	58	Primary lt indirect, scrotal		Prostatic hyper- trophy	12/15/38	None	Thrombophlebitis, rt leg	None	4/10/40—well
A-09636	57	Primary lt indirect		Hypertension Chronic cardio- vascular dis- ease	1/10/39	None	Auricular fibrilla- tion Diffuse bronchitis	None	4/10/40— femoral re- currence
A-15821	53	Recurrent rt direct and indirect, slid- ing	One	Slight pulmon- ary emphysema	3/17/39	None	Bronchopneu- monia	None	4/10/40—well
A-6795	37	Recurrent rt indirect	Two	None	10/20/39	None	Bronchopneu- monia Pulmonary tuber- culosis(?)	None	4/10/40—well
A-25507	37	Recurrent rt direct	One	None	11/ 6/39	None	None	None	Unable to lo- cate patient
A-34208	72	Primary rt indirect, scrotal, and rt femoral		None	11/ 8/39	None	None	None	4/18/40—well
A-25507	37	Recurrent lt direct	One	None	11/21/39	None	None	None	Unable to lo- cate patient
A-34888	58	Primary lt direct		None	12/21/39	None	Wound infection— <i>Staph aureus</i>	None	4/10/40—well
A-15821	54	Primary lt direct		Slight pulmon- ary emphysema	12/27/39	None	None	None	4/10/40—well

TABLE I (Continued)

History Number	Age	Type of Hernia	Previous Repairs	Concurrent Diseases	Date of Operation	Operative Accidents	Postoperative Complications	Later Complications	Result
A-35330	51	Recurrent rt direct	Two	None	1/ 6/40	Division of spermatic artery	Edema of testicle	None	4/10/40—well
A-11085	66	Primary rt direct and indirect, partly sliding		Prostatic hypertrophy, partial urinary retention	2/29/40	None	Edema of testicle	None	
A-36381	39	Recurrent lt indirect, partly sliding	One	None	3/ 1/40	None	Bronchitis	None	
A-31388	60	Primary rt direct and indirect		Pulmonary emphysema Prostatic hypertrophy	3/ 2/40	None	Atelectasis, right lower lobe	None	
A-31390	45	Primary rt direct		None	3/27/40	None	None	None	
A-14208	62	Primary rt direct		Hypertensive cardiovascular disease	3/29/40	None	None	None	
A-32284	49	Primary rt indirect, scrotal		Hypertensive cardiovascular disease Pulmonary emphysema Syphilis Obesity	4/ 2/40	None	None	None	
A-36480	45	Primary rt indirect			4/17/40	None	None	None	

On the surgical services of St Luke's and New York Hospitals, transplantation of the cord to the femoral canal has been carried out in the repair of 33 inguinal herniae affecting 27 individuals since June 24, 1937 (Table I). Twenty-one herniae were primary and 12 were recurrent. Nineteen of the total number have been followed more than one year after operation, five have recurred, an incidence of approximately 26.3 per cent. In the group of 12 primary herniae, followed more than one year, there were four recurrences, or 33.3 per cent. One of the four recurrences was femoral and the remaining three were inguinal. Two of the inguinal recurrences were in one individual who had bilateral herniae (Table II). In the group of seven recurrent herniae, followed more than one year after operation, there was one recurrence, or approximately 14 per cent. This one recurrence was femoral in type and occurred in a patient who, at the time of operation, had a primary femoral as well as a recurrent inguinal hernia on the side of the subsequent recurrence (Table III). The remaining cases of the total series of 33 cases have been operated upon too recently to have any statistical value.

The apparent merits of the operation are

(1) That it permits a complete closure of the inguinal defect without damage to the cord or testicle.

(2) It does not require any special incision or special materials.

(3) It can be applied to any type of inguinal hernia without impairment of the advantage gained by elimination of the cord as an obstacle to repair.

The most obvious disadvantages of the procedure are

(1) Exposure of the pubic ligament is difficult in obese patients. Goinard¹⁸ suggests use of the Reverdin needle for the placing of sutures in this ligament.

(2) It involves a detachment of the inguinal ligament. This ligament is ordinarily thought of as the sheet anchor in hernial repair and it is not heedlessly jeopardized. After the ligament has been resutured, however, one cannot doubt its stability.

(3) The advantage gained in being able to completely close the inguinal defect is offset to some extent by the necessity of opening the femoral ring. Presumably, this may give rise to a weakness at the femoral opening comparable to that produced by a femoral hernia.

It is a matter of general experience, however, that femoral hernia is less likely to recur than inguinal hernia. The incidence of recurrence in the adult males of the series reviewed by Coley²⁰ was 8.7 per cent for indirect, 16.4 per cent for the direct, and 11.9 per cent for the combined type of direct and indirect inguinal herniae; the recurrence rate for femoral hernia in the adult male was 9.1 per cent. Watson²¹ states that 5 to 10 per cent of the indirect inguinal herniae recur, depending upon the age of the patient and the choice of operation, and that recurrences after operations for direct herniae are from 10 to 20 per cent in the hands of the most experienced operators; he places the rate of recurrence of femoral herniae, following the usual methods of repair, at slightly less than 5 per cent. This ratio of recurrence between in-

TABLE II
PRIMARY HERNIAE FOLLOWED MORE THAN ONE YEAR AFTER REPAIR, 12 CASES

History Number	Age	Type of Hernia	Concurrent Diseases	Date of Operation	Operative Accidents	Postoperative Complications	Later Complications	Result
124-073	63	Primary rt indirect, scrotal	Diabetes Arteriosclerosis Chronic myo- carditis	9/29/37	None	None	None	10/25/38—well 11/29/39—died suddenly No recurrence of hernia
148638	61	Primary rt direct	Obesity Arteriosclerosis Urinary incon- tinence	10/ 5/37	None	None	None	4/7/40—well
156798	51	Primary rt direct	None	10/14/37	None	None	None	4/7/40—well
210770	63	Primary rt direct	Prostatic hyper- trophy	8/13/38	None	None	None	4/21/40—well
1080 129-530	51	Primary rt direct	None	8/17/38	None	None	None	4/24/40—well
210770	63	Primary lt direct	Prostatic hyper- trophy	8/30/38	None	None	None	4/21/40—well
218169	56	Primary rt direct	Obesity	11/ 5/38	None	None	None	4/14/40—well
218977	51	Primary rt direct	Chronic bron- chitis	11/ 8/38	None	None	None	6/18/39—inguinal recurrence
218169	56	Primary lt direct	Obesity	11/19/38	None	Wound infection— <i>Staph aureus</i>	Delayed healing	4/14/40—inguinal recurrence
218977	51	Primary lt direct	Chronic bron- chitis	11/21/38	None	None	None	6/18/39—inguinal recurrence
A-10382	58	Primary lt indirect, scrotal	Prostatic hyper- trophy	12/15/38	None	Thrombophlebitis, rt leg	None	4/10/40—well
A-09636	57	Primary lt indirect	Hypertension Chronic cardio- vascular dis- ease	1/10/39	None	Auricular fibrilla- tion Diffuse bronchitis	None	4/10/40—femoral recurrence

TABLE III
RECURRENT HERNIAE FOLLOWED MORE THAN ONE YEAR AFTER REPAIR, SEVEN CASES

History - Num- ber	Age	Type of Hernia	Previous Repairs	Concurrent Diseases	Date of Opera- tion	Operative Accidents	Postoperative Complications	Later Compli- cations	Result
122-742	39	Recurrent It indirect, sliding—en- tire sigmoid	Two	None	6/24/37	Division of spermatic artery	None	Atrophy of testicle	4/10/40—well
123-653	67	Recurrent It indirect— incarcerated omentum	One	Chronic bron- chitis	8/31/37	None	Exacerbation of bronchitis—cough	None	4/6/40—well
209321	50	Recurrent It indirect Primary It femoral	One	Chronic bron- chitis	7/23/38	None	Cough	None	4/7/40— femoral re- currence
209321	50	Recurrent rt indirect	One	Chronic bron- chitis	8/ 4/38	None	Cough	None	4/7/40—well
129-680	49	Recurrent rt direct	One	None	8/23/38	None	None	None	4/12/40—well
81047	48	Recurrent It direct	Four	Syphilis	10/18/38	Division of spermatic artery	Edema of testicle	Atrophy of testicle	4/7/40—well
A-15821	53	Recurrent rt direct and indirect, slid- ing	One	Slight pulmon- ary emphysema	3/17/39	None	Bronchopneu- monia	None	4/10/40—well

guinal and femoral herniae is sometimes reversed. Glenn,²² for example, in a series of cases from New York Hospital, found the incidence of recurrence higher in femoral than in inguinal herniae. In general, the advantage gained in being able to completely close an inguinal defect would appear to outweigh the disadvantage of producing a possible weakness at the femoral ring.

There is no reason to suppose, however, that transfer of the cord to the femoral canal will preclude its becoming a pathway for recurrence, and in two instances, already, a hernial sac has appeared in the femoral region lateral to the cord (Cases No 209321 and No A-09636). There is some clinical indication that the femoral recurrences are of the prevascular type described by Moschcowitz,²³ Cevaino,²⁴ Keynes²⁵ and others.

The results of the operation, so far, do not warrant unstrained optimism or complete condemnation. In estimating its value one must take into consideration the types of hernia for which it was employed. It was not undertaken in simple herniae in young patients because the operations in current use yield satisfactory results in cases of this kind. The group of 21 primary herniae, in which the operation was employed, consisted of 13 direct, four indirect scrotal, two simple indirect, one combined direct and indirect, and one direct, indirect and sliding combined. The ages of the primary group ranged from 45 to 72 years, the average being 57 years. In the recurrent group, 12 in number, there were five direct, four indirect, one of which was incarcerated, one indirect sliding, one indirect partly sliding, and one direct and indirect sliding hernia. The ages of the recurrent group ranged from 37 to 67 years of age, the average being approximately 46 years.

It is clear that the results of treatment in herniae of the kind described cannot be compared with studies which include a large proportion of less difficult types. The small series herein presented is perhaps most comparable with the cases reviewed by Grace and Johnson.²⁶ This review dealt with the results of hernioplasty in 1,032 patients, all of whom were more than 50 years of age. The incidence of recurrence in this large group was 25.8 per cent for primary, and 34 per cent for recurrent inguinal herniae.

The number of cases in which the cord has been transplanted to the femoral canal is not sufficiently large, and the period of observation is not long enough, to permit any conclusions as to the ultimate value of the procedure. The operation appears to be sound in principle. Further experience should reveal its weak points and possibly suggest means of correcting them.

REFERENCES

- ¹ Bassini, Edoardo. *Nuovo metodo operativo per la cura radicale dell'ernia inguinale*. 19 pp., 4 colored plates, Padova, 1889.
Idem. *Über die Behandlung des Leistenbruches*. *Arch f klin Chir*, 40, 429-476, 1890.
Idem. *Scritti di Chirurgia erniaria*. Tipografia del Seminario di Padova, 1, 3-30, 1937.
- ² Halsted, W. S. *The Radical Cure of Hernia*. *Johns Hopkins Hosp Bull*, 1, 12-13, 1890.
- ³ Halsted, W. S. *The Radical Cure of Inguinal Hernia in the Male*. *Johns Hopkins Hosp Bull*, 4, 17-24, 1893, also *ANNALS OF SURGERY*, 17, 542-556, 1893.

- ⁴ Coley, W B The Operative Treatment of Hernia in Children with a Report of 133 Cases Amer Jour Med Sci, 109, 487-499 1895
- ⁵ Ferguson, A H Oblique Inguinal Hernia J A M A, 33, 6-14, July 1, 1899
- ⁶ Halsted, W S The Cure of the More Difficult as Well as the Simpler Inguinal Ruptures Johns Hopkins Hosp Bull, 14, 208-214, 1903
- ⁷ Torek, F Inguinal Hernia An Operative Method by Which Close to 100 Per Cent Cures Have Been Obtained ANNALS OF SURGERY, 70, 65-80, 1919
- ⁸ Quain, E P The Technique of Inguinal Herniotomy Surg, Gynec and Obstet, 30, 88-92, January, 1920
- ⁹ Skillern, P G, Jr The Choice of Operation in Inguinal Hernia Surg, Gynec and Obstet, 34, 230-237, February, 1922
- ¹⁰ Erdman, S Hernia Nelson New Loose-Leaf Surgery, Chap 6, 589-668A New York, London, etc, Thomas Nelson and Sons, 1937
- ¹¹ Burdick, C G, and Higinbotham, N L Division of the Spermatic Cord as an Aid in Operating on Selected Types of Inguinal Hernia ANNALS OF SURGERY, 102, 863-874, November, 1935
- ¹² Cheever, D Discussion of Papers on Hernia Trans Amer Surg Assn, 41, 351, 1923 Philadelphia, William J Dornan, 1923
- ¹³ Seelig, M G, and Chouke, K S A Fundamental Factor in the Recurrence of Inguinal Hernia Trans Amer Surg Assn, 41, 315-324, 1923, also Arch Surg, 7, 553-572, November, 1923
- ¹⁴ Mathews, F S Hernia through the Conjoined Tendon or Hernia of the Linea Semilunaris ANNALS OF SURGERY, 78, 300-304, August, 1923, also Trans Amer Surg Assn, 41, 325-330, 1923
- ¹⁵ Gallie, W E, and Le Mesurier, A B The Use of Free Transplants of Fascia as Living Sutures in the Treatment of Hernia Trans Amer Surg Assn, 41, 331-348, 1923, also Arch Surg, 9, 516-529, November, 1924
- ¹⁶ Fauntleroy, A M Development of an Inguinal Hernia through the Femoral Ring Following the Descent of the Testicle by the Same Route ANNALS OF SURGERY, 72, 675, December, 1920
- ¹⁷ Cooper, Sir Astley P The Anatomy and Surgical Treatment of Abdominal Hernia Part I, 8, 2nd ed, C Aston Key, London, Longman, Rees, Orme, Brown, and Green, 1827
- ¹⁸ Goinard, P Cure radicale de certaines hernies inguinales par fixation du tendon conjoint au ligament de Cooper Presse Med, 47, 872, May 31, 1939
- ¹⁹ Lisitsyn, M S Transplantation of the Spermatic Cord into the Femoral Canal in Operations for Recurrent Hernias Vestnik khir, 34, 163, 1934
- ²⁰ Coley, B L Three Thousand Consecutive Herniotomies with Special Reference to Recurrence, Based on 837 Followed Cases ANNALS OF SURGERY, 80, 242-255, August, 1924
- ²¹ Watson, L F Hernia, 2nd ed, 211, 316 St Louis, C V Mosby Co, 1938
- ²² Glenn, F The Surgical Treatment of Five Hundred Herniae ANNALS OF SURGERY, 104, 1024-1029, December, 1936
- ²³ Moschcowitz, A V Prevascular Femoral Hernia ANNALS OF SURGERY 55, 848-856, 1912
- ²⁴ Cevario, L Ernia crurale pievascolare intravaginale ed ernia crurale commune omologa Arch Ital di Chir, 3, 145-153, March 5, 1921
- ²⁵ Keynes, G Prevascular Femoral Hernia Brit Jour Surg, 20, 55-57, July, 1932
- ²⁶ Grace, R V, and Johnson, V S Results of Herniotomy in Patients of More Than Fifty Years of Age ANNALS OF SURGERY, 106, 347-362, September, 1937

DISCUSSION—DR WILLIAM E GALLIE (Toronto, Can) I think we will all admit that the subject that Doctor MacFee has presented to us is very ingenious and very interesting from an anatomic standpoint I must

confess that I was surprised to learn that the inguinal ligament could be detached from the pubic spine and sewn back in position with a restoration of the normal strength of the ligament. I would rather have expected that the ligament would remain relaxed and weak and in that way perhaps lessen the effectiveness of the attempt to cure a large recurring inguinal hernia. However, he assures me that this is not so and that actually the inguinal ligament does feel as strong as ever.

It is somewhat disturbing to find so many recurrences after the operation, but, of course, one who performs many hernioplasties must expect recurrences in large ones and particularly those who have had operations before, I suppose the place that this operation will occupy in our surgical technic will depend on experience with a large number of cases.

There are, of course, other ways of curing large recurring inguinal herniae, but I do not think it is the appropriate time to enter into that discussion, but there is one place, however, where I think this type of operation is eminently suitable. You will recall that some months ago Doctors Burdick and Coley published a paper in which they stated that they had failed to master the technic of using fascia. Now, of course, to get over the difficulty of not using fascia, because one could hardly expect them to use it, they suggested the removal of the testis and the spermatic cord in order to make the closure of the canal more easily completed. Well, it occurs to me that this is exactly the place where Doctor MacFee's procedure would be useful. When anybody feels the urge to remove the testis and the spermatic cord he should give some consideration to the suggestions that Doctor MacFee has made to-day.

THE PROBLEM OF PRODUCING COMPLETE AND LASTING SYMPATHETIC DENERVATION OF THE UPPER EXTREMITY BY PREGANGLIONIC SECTION *

REGINALD H. SMITHWICK, M.D.

BOSTON, MASS

FROM THE SURGICAL SERVICES AND PERIPHERAL VASCULAR CLINIC OF THE MASSACHUSETTS GENERAL HOSPITAL, BOSTON, MASS

DURING the past five years (January 24, 1935–May 1, 1940) we have sympathectomized 151 upper extremities by preganglionic section for the relief of vascular spasm. We turned to this procedure because the results of cervicodorsal ganglionectomy, postganglionic section, had not been satisfactory.^{1, 2} We felt that as the effects of preganglionic denervation of the lower extremity had been gratifying, there was reason to expect similar improvement if the upper extremity could be sympathectomized in a like manner.

Two difficulties have been encountered in dealing with the upper extremity which makes its successful denervation more of a problem than the lower. First, the question arises as to whether the upper extremity can be adequately sympathectomized by interruption of preganglionic pathways. Second, the matter of regeneration has given us more concern. The first question pertains to immediate results, the second to late results.

To obtain satisfactory immediate results, one must thoroughly interrupt the sympathetic pathways concerned. If sufficient residual innervation exists, this will be reflected in the clinical result. The sympathetic nerve supply to the upper extremity (Fig. 1) has been variously described,^{3, 4} so that one must assume that preganglionic pathways may arise from the first to the tenth dorsal segments of the cord. The relative importance of each is unknown. The postganglionic pathways are more localized, and run from the middle cervical to the second dorsal ganglia, inclusive, to the brachial plexus. From these data it is apparent that all possible preganglionic pathways can be interrupted without dividing postganglionic fibers, with the exception of the outflow from the first dorsal segment. The latter can be abolished either by section of the first dorsal white ramus, without cutting the gray ramus, or by intraspinal section of the first dorsal anterior root. Neither of these procedures appears feasible.

We, therefore, elected to denervate the upper extremity (Fig. 2) by dividing the preganglionic outflow to the second and third dorsal ganglia of the sympathetic trunk, and sectioning the latter below the third ganglion.⁵ The necessary exposure is obtained through a small vertical paravertebral incision, resecting the inner portion of the third rib and transverse process. This technic has been termed ramisectomy. A similar operation has been reported by Telford⁶ who, however, uses the anterior approach.

If this operation is accurately performed, we have never been able to

* Read before the American Surgical Association, St. Louis, Mo., May 1, 2, 3, 1940.

demonstrate the presence of residual sympathetic nerve supply to the upper extremity of clinical significance. In other words, it seems quite definite that the outflow from the first dorsal segment is unimportant. This conclusion is supported by Simmons and Sheehan,^{7, 8} who have studied many of Telford's

cases after operation. It is further supported by our earlier experiences in which we found that the upper extremity could be thoroughly sympathetomized by excision of the second and third dorsal sympathetic ganglia and intervening trunk.

If this operation is not accurately performed, incomplete sympathetomy may result. This may be due to failure to interrupt the white ram of the second or third dorsal segment or by failure to interrupt the trunk itself. We thought that by resecting the portion of the second and third intercostal nerves from which the rami arise the first possibility would be eliminated. However, in our earlier cases a number of incompletely denervated extremities resulted (Fig 3). Subsequent study and reoperation revealed that the original operation had not been complete because of failure to interrupt the outflow from the second or third dorsal segment. The most likely explanation appeared to be that the technic did not necessarily insure division of the white ram of the two segments. We, also, soon became aware of a second difficulty because some of the extremities, which were completely denervated, began to show definite signs of regeneration, often as quickly as six months after operation.

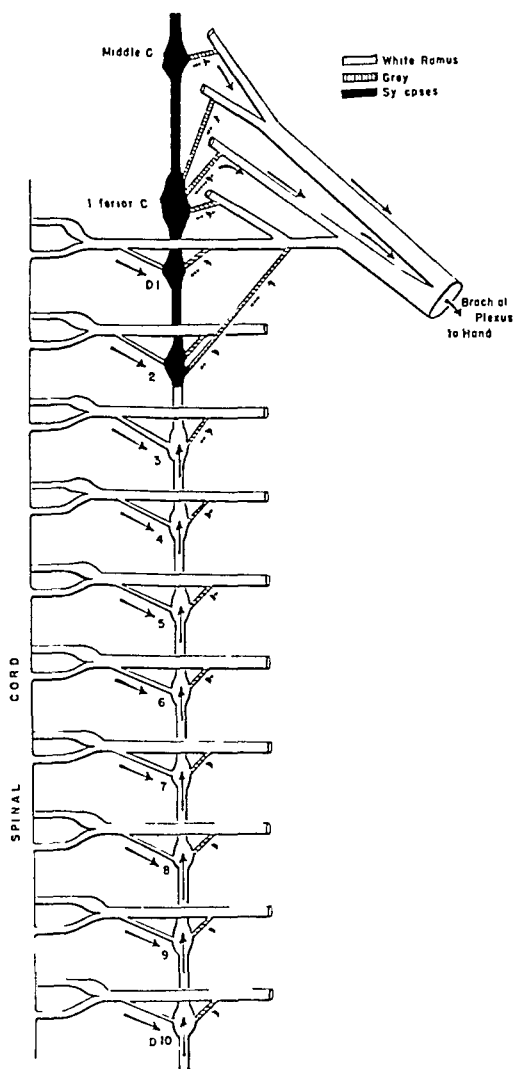


FIG 1.—Preganglionic pathways to the arm have been described as arising from the first to the tenth dorsal segment of the cord. We have not found the outflow from D1 to be of clinical importance. That from D2 and D3 is very important in some cases, and apparently of less importance in others.

For these reasons, the technic was changed (Fig 4), both to insure complete denervation and to further guard against regeneration. In this modification, called extraspinal root section, the second and third intercostal nerves were resected from the lateral portion of the operative field inward, dividing the posterior and anterior roots separately at a point just proximal to the posterior root ganglion. This maneuver has been successful in pre-

venting incomplete denervation because it is impossible to fail to divide the white communicating ramus when the anterior roots are always sectioned at a point proximal to their origin. It has been helpful, also, in delaying the appearance of regeneration in most instances, in preventing it in some, and in minimizing it in others. While excellent late-results have been obtained, the majority of extremities which have been denervated in this manner do show evidence of regeneration as years pass by (Fig. 5).

This is readily demonstrated by following the course of the surface temperature of a finger tip in a cool environment as time goes on, and if a fall

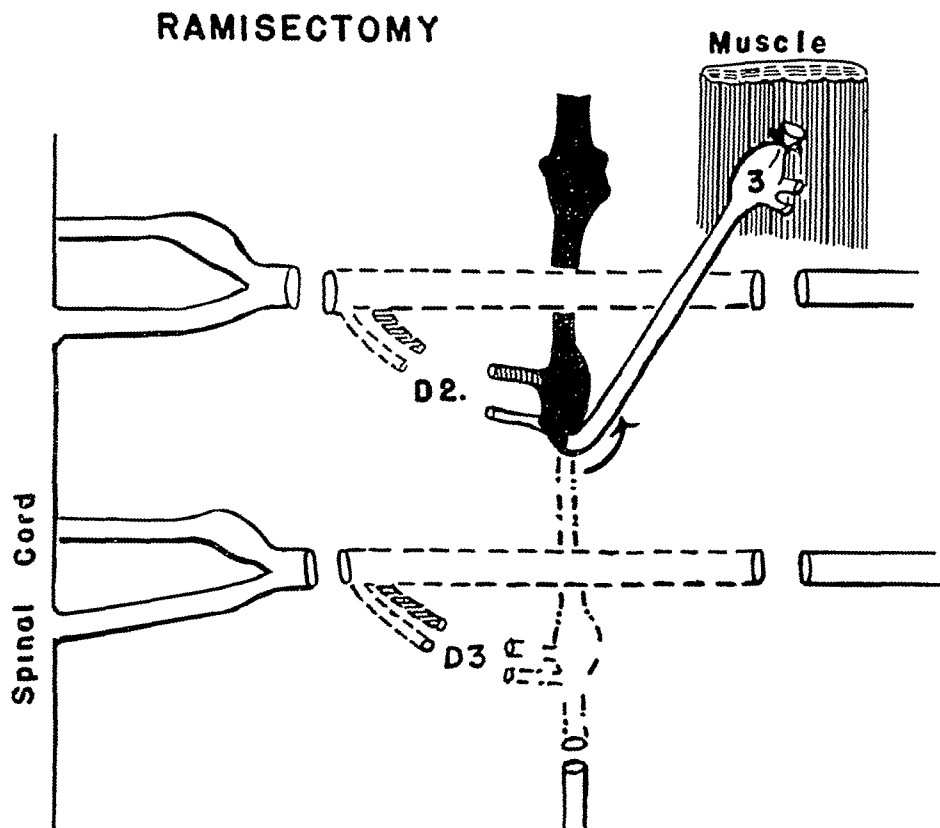


FIG. 2—The first type of preganglionic sympathectomy was termed ramisection. The communicating rami of D2 and D3 were divided and that portion of the intercostal nerves from which they arise was resected. The sympathetic trunk was divided below D3.

is noted, observing the subsequent rise to the previous level after regenerated pathways are temporarily interrupted again by novocain block of the appropriate peripheral nerves.

Feeling that the sectioned anterior roots of D2 and D3 were more likely sources of regenerating fibers than the cut end of the sympathetic trunk, the operation was further modified and termed intraspinal root section (Fig. 6). Having accidentally discovered that a large portion of the intraspinal part of the anterior root could be removed by separating the attachment of the arachnoid and then gently teasing the root out, this appeared to be a feasible routine procedure. A spinal fluid leak of no consequence results. It seemed unlikely that the proximal cut end of the roots would regenerate after the meninges

*J S Right Fifth Finger Tip
Illustrating Incomplete Sympathectomy and Repeated Regeneration from D₂ and D₃
after Repeated Division of Trunk and Rami*

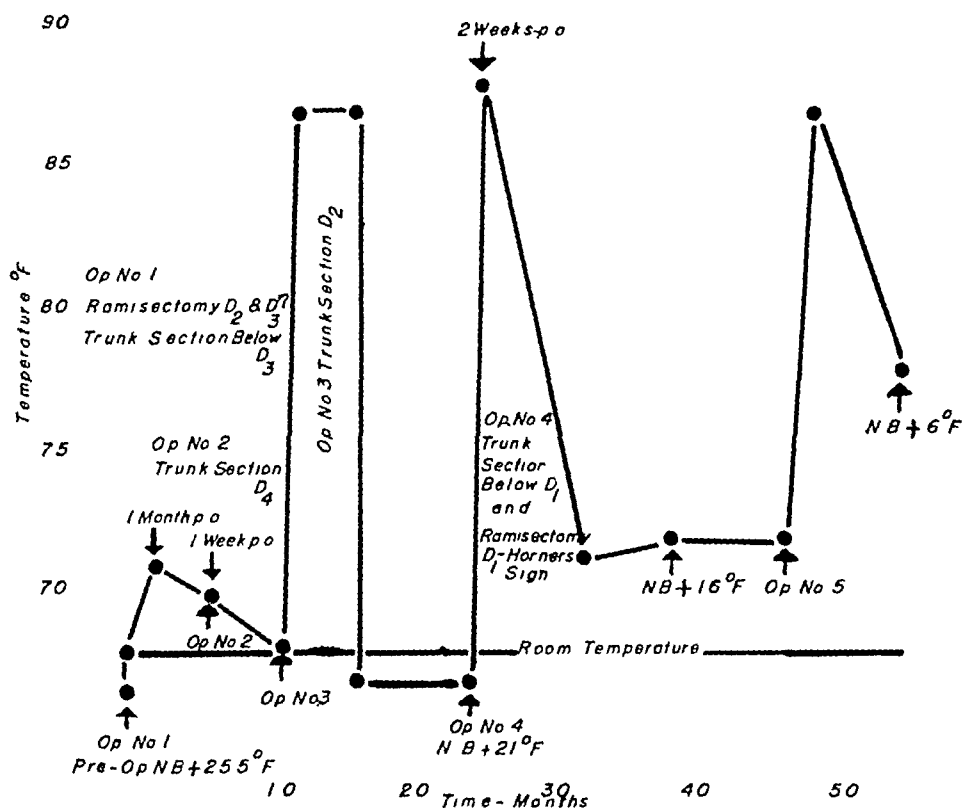


FIG 3—The surface temperature of a finger tip when exposed to a cool environment is followed over a period of five years. The first two operations were incomplete and no significant temperature rise resulted. The extremity was then sympathectomized three times by trunk section above D₂. Regeneration has taken place after each operation in six months or slightly more. The importance of the outflow from D₂ and D₃ is brought out in this case. Operation No 5 was trunk section below C₃ by anterior approach.

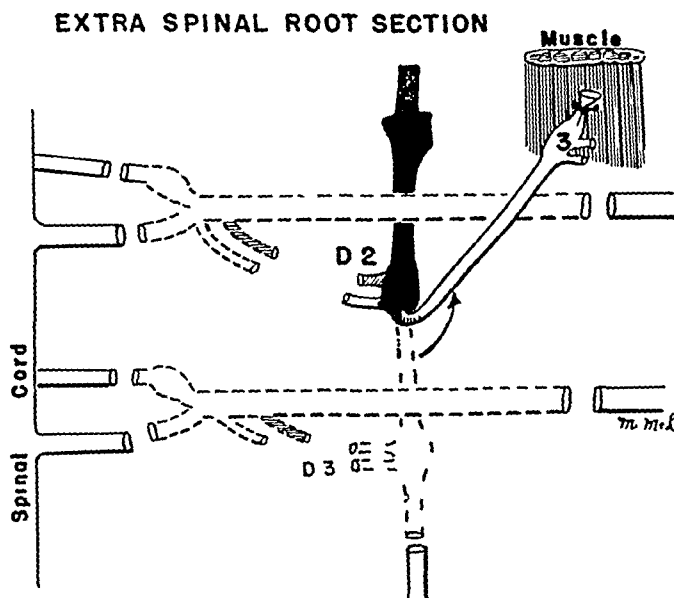


FIG 4—This first modification was made to insure interruption of the white rami from D₂ and D₃ by cutting the anterior roots proximal to the point of origin of the rami from the intercostal nerves. It is referred to in the text as extra-spinal root section.

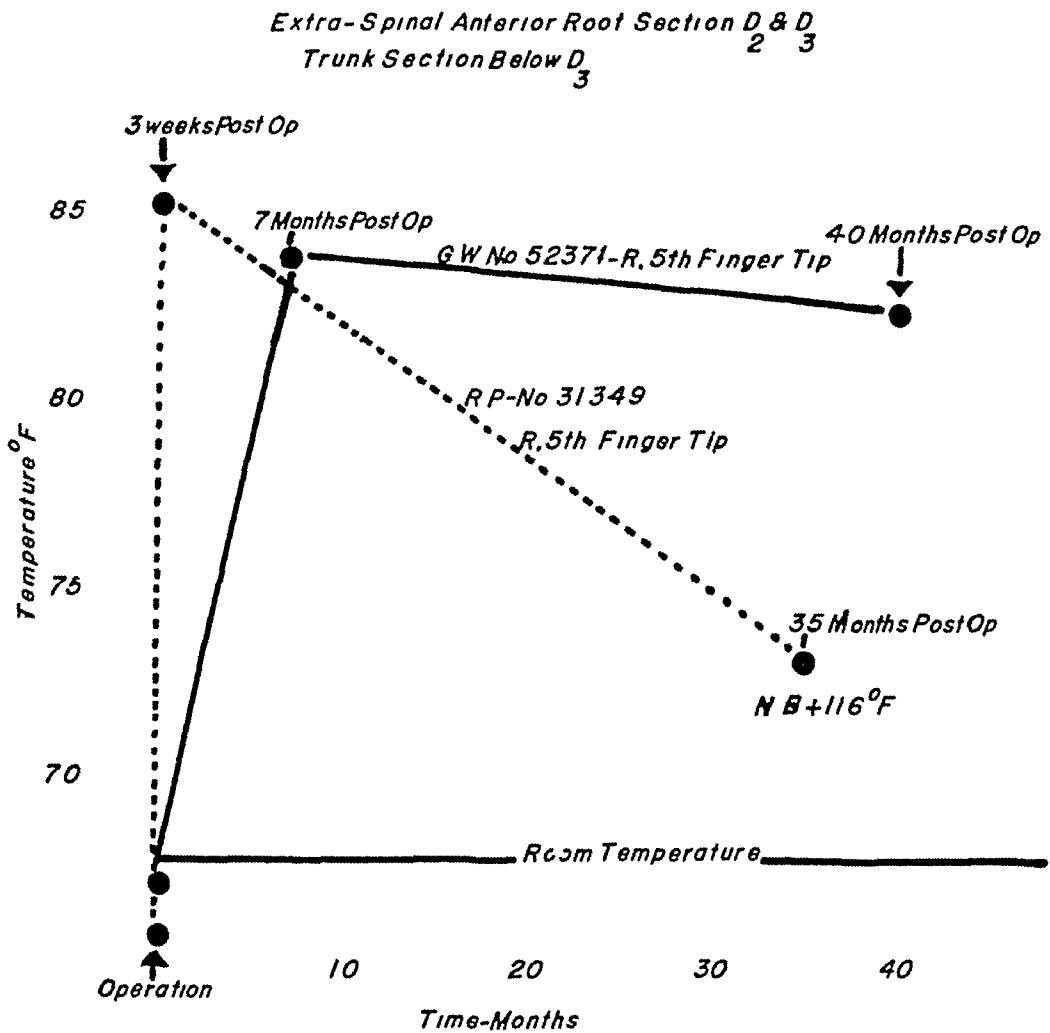


FIG 5—The surface temperature of a finger tip in a cool environment is followed after extraspinal root section. The same operation has been performed in each extremity (two different patients). In one instance, regeneration has taken place. In the other there is no evidence of regeneration.

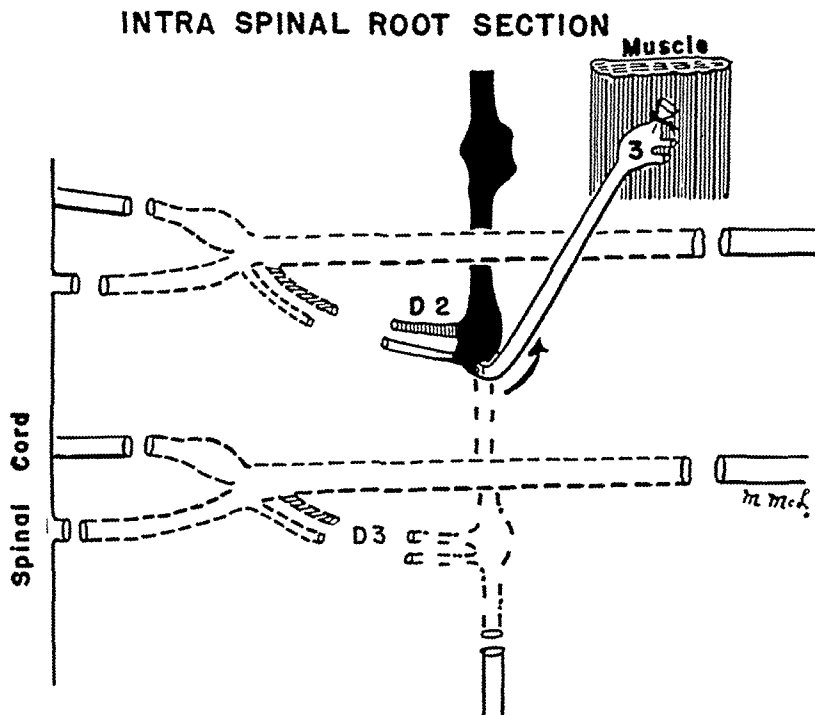


FIG 6—This second modification also relates to the management of the outflow from D₂ and D₃. The anterior roots are divided within the arachnoid so that the proximal cut end lies within the spinal canal rather than in the paravertebral space. It is termed intraspinal root section. It is thought to be an additional safeguard against regeneration in cases in which the outflow from D₂ and D₃ is important.

had healed (Fig 7), because they would be contained within a water-tight compartment. The immediate effect of this operation has always been most satisfactory and complete (Fig 8). Excellent late-results, of from two to three years' standing, also exist, but in a number of instances, moderate to marked evidence of regeneration has been detected. This, however, is usually delayed as compared with lamisectomy, and is noticed during the second year in most instances.

Some cases have had one extremity denervated by extraspinal root section and the other by intraspinal root section (Figs 9, 10 and 11). As a rule, the results of the latter type of operation are superior, suggesting that intraspinal anterior root section is an additional safeguard against regeneration.



FIG 7—Photograph of actual specimens of the second and third intercostal nerves which have been removed photographed beside a centimeter rule. A liberal extent of the intraspinal portion of the anterior roots is resected. The posterior root with its ganglion and the point of origin of the communicating rami from the intercostal nerves are visible.

An examination of the possible sources of regenerating fibers (Fig 12) reveals the fact that only a few centimeters separate these from the decentralized sympathetic trunk. It seems most likely that the regenerating fibers unite with the sympathetic trunk at the second dorsal ganglion, which is not materially displaced. We have repeatedly resympathectomized regenerated extremities by sectioning the sympathetic trunk again between the first and second dorsal ganglia.

The variable results following the same operation in different patients, and different operations in the same patient, are best explained by assuming that wide variations in the origin of preganglionic pathways exist. If they come chiefly from the second and third dorsal segments, which we have proven to be the case in a number of instances, and suspect to be the case in

Intra-Spinal Anterior Root Section D₂ & D₃
Trunk Section Below D₃

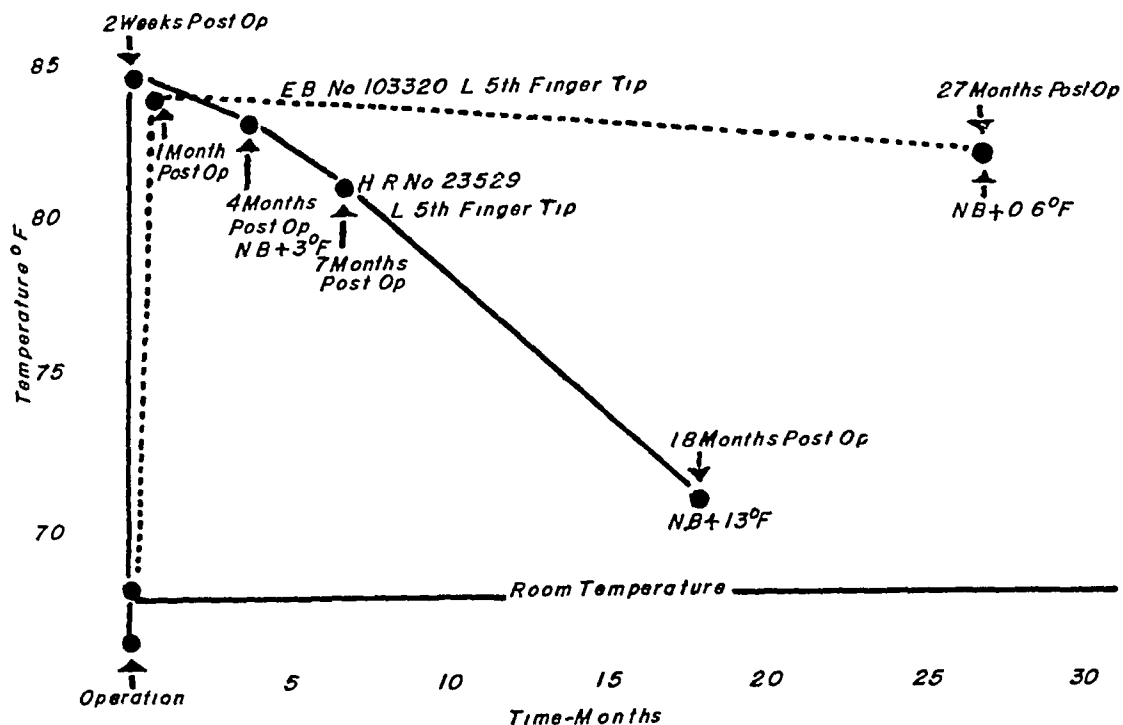


FIG 8—The late result of intraspinal root section is compared in two different patients. In one instance there is little evidence of regeneration. In the other, considerable regeneration has occurred. This probably has come largely from the sectioned end of the sympathetic trunk. It seems reasonable to believe that the outflow from D₂ and D₃ was not particularly important in the regenerated extremity.

R S-Group I- 18 Months Post Op
Illustrating Regeneration from D₃

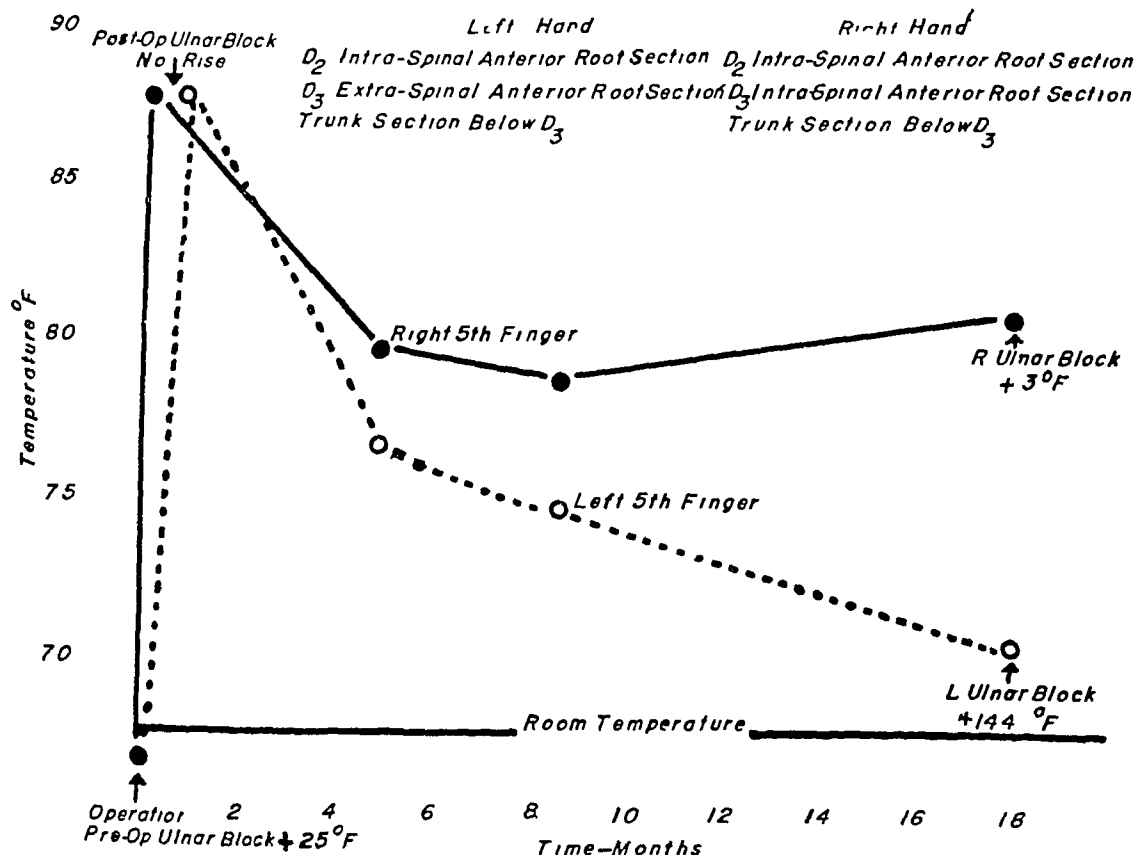


FIG 9—The late results of different operations upon the two extremities of the same patient are contrasted. If it is safe to assume that the nerve supply to the arms is similar in the same case then it is reasonable to believe that the difference in the results is due to regeneration from D₃ in this particular case. Intra-spinal root section appeared to be more effective than extra-spinal root section.

the majority, great pains must be taken with the management of these two segments. One may suspect at operation, that this is the case if the sympathetic trunk is very small. If on the other hand, the motor supply arises chiefly from lower dorsal regions of the cord, it probably makes less difference how the outflow from the upper cord is handled, and more attention must be given to the lower sectioned end of the sympathetic trunk. Obviously, simple division is not sufficient, for although this point may be as far as 5 cm

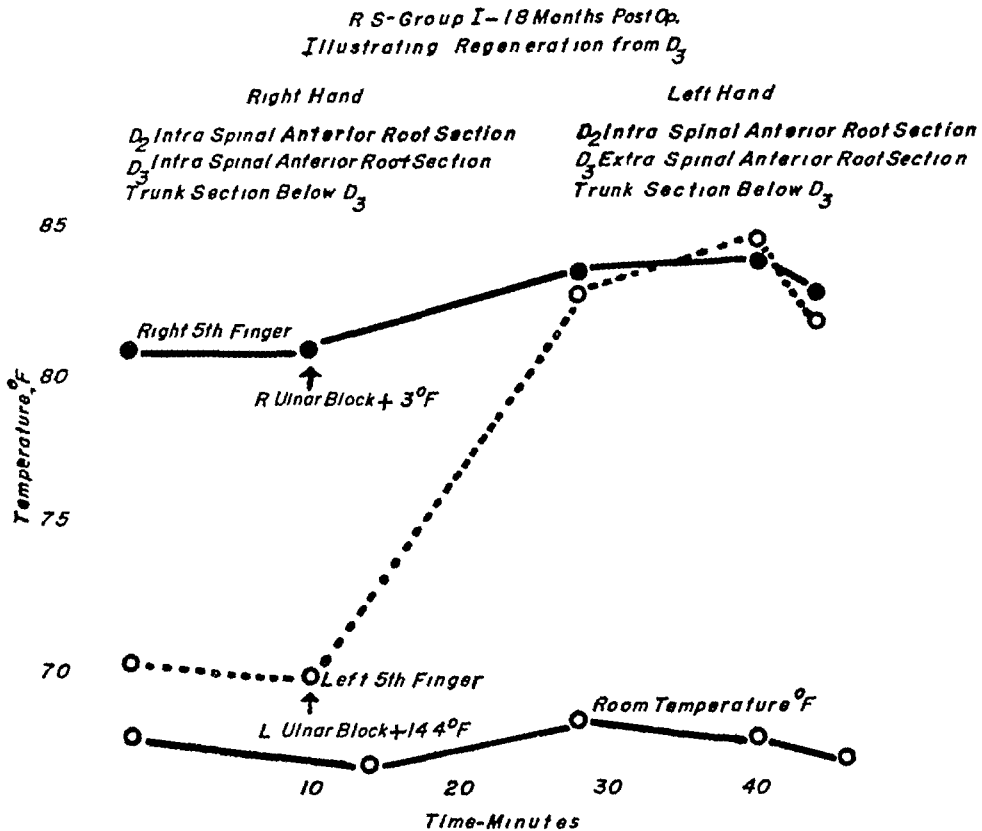


FIG. 10.—This is the same case as is illustrated in Figure 9. After novocain block of the ulnar nerves the surface temperature of the fifth finger tips reaches the same high level showing that any cooling which has taken place is due to nerve regeneration and not to progress of the disease. This is the usual explanation of cooling in our experience, when studying late results.

away from the decentralized second dorsal ganglion, sympathetic fibers appear to have little difficulty in traversing this distance.

To further guard against regeneration (Fig. 13), during the past year we have carefully ligated the distal, divided end of the sympathetic trunk, a precaution which we had not formerly taken, in conjunction with the intra-spinal type of anterior root section of the second and third dorsal segments. More recently, being dubious as to whether ligation of the sympathetic trunk will prove to be effective in preventing regeneration from this source, and to further guard against regeneration from D₂ and D₃, we have covered the decentralized second and third ganglia and intervening trunk with a fine silk cylinder. We hope that the dense scar tissue capsule, which Page⁹ has found

to form in three weeks when silk is wrapped about the kidney, heart or liver, and which he believes is impervious to vessels and nerves, will form under these circumstances and prove effective in further minimizing regeneration from any of the possible sources. How successful these measures will be cannot be determined for another year or two.

Our present feeling about this problem is that the immediate and early results of preganglionic denervation of the upper extremity are uniformly satisfactory and worth while. The degree of tissue damage, or local fault, already present, is the chief limiting factor. The same is often true of the late-results, but too frequently cooling of the extremity is noted when

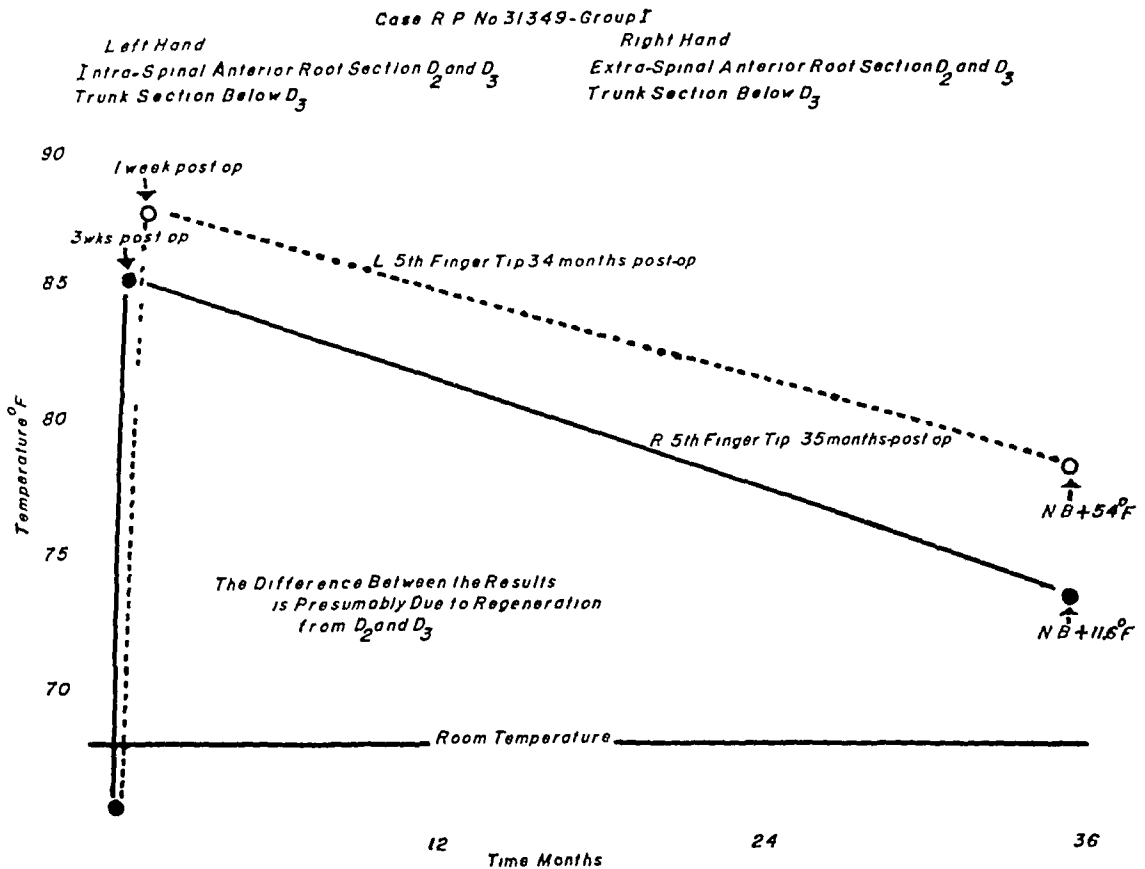


FIG 11—The late result of intraspinal root section on one extremity is compared with extra spinal root section on the opposite extremity of the same patient. A minor degree of regeneration has taken place in the former and moderate degree in the latter. Again intraspinal root section appears to be more effective. This is usually but not always so suggesting that the outflow from D_2 and D_3 is frequently important. If, however, the outflow in a given case comes chiefly from lower dorsal levels, there would be no material difference between the two types of operation, and regeneration, if it took place, would come from the sectioned sympathetic trunk.

examined as years pass by. In the great majority of such instances this can be shown to be caused by regeneration. This may be sufficient to materially detract from the result, although one rarely finds a patient who has not benefited by operation. Even in the presence of moderate to marked regeneration (Fig 14) patients find their symptoms milder and easier to control. A study of the circulation of such extremities, as judged by surface temperature levels in a cool environment, reveals why this is so. The regenerated extremity falls somewhere between the unoperated and the completely denervated arm. The blood flow is well sustained from the shoulder to the middorsum of the hand

PATHWAY OF REGENERATING FIBERS

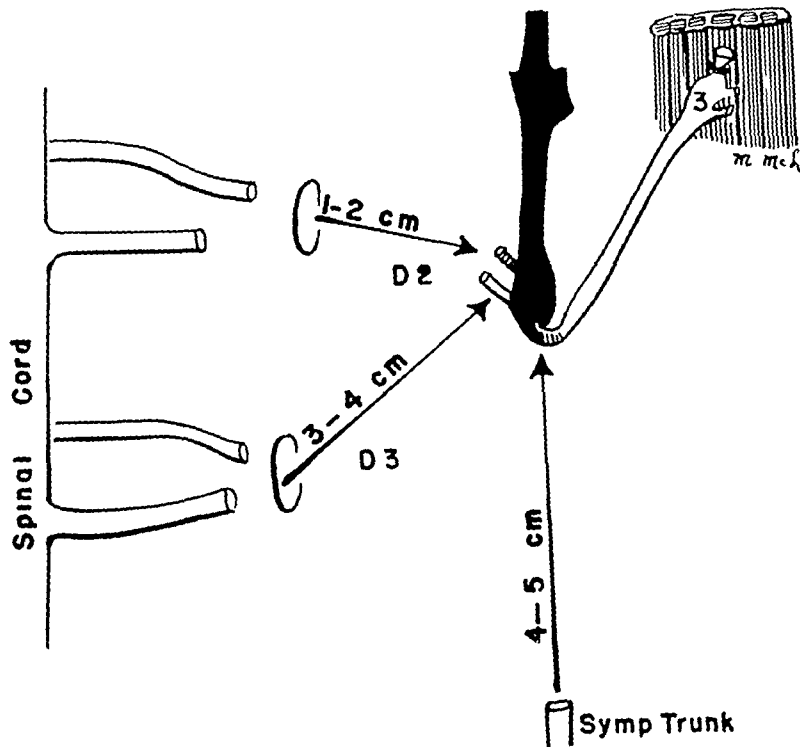


FIG 12—Only a few centimeters separate the three areas from which regenerating fibers may come and the decentralized but undisplaced, second dorsal ganglion the point where anastomosis presumably takes place. Sympathetic fibers apparently have no difficulty in covering these short distances.

INTRA SPINAL ROOT SECTION

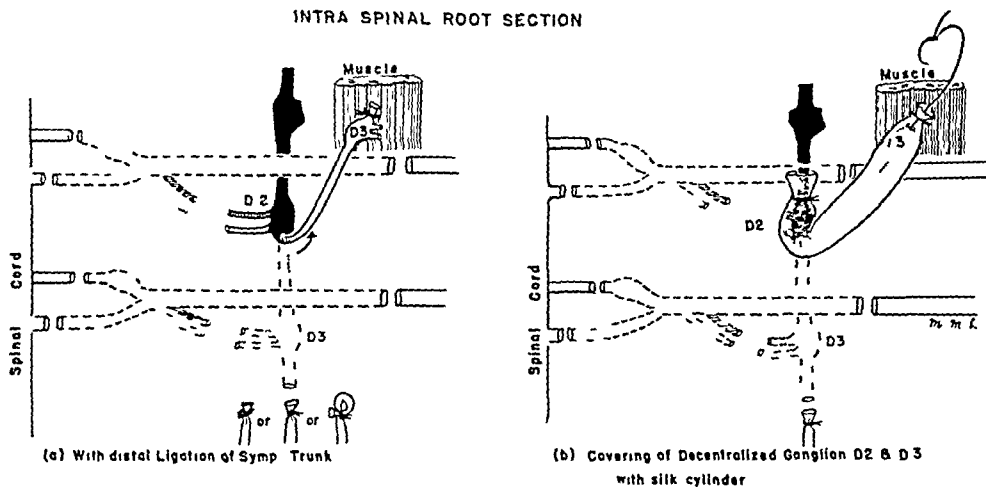


FIG 13—Our present technic combines intraspinal anterior root section with ligation of the distal end of the divided sympathetic trunk. More recently, the decentralized second and third ganglia and intervening trunk have been covered with a fine silk cylinder to further guard against regeneration.

Even in the presence of marked regeneration the base and midfinger temperature levels are quite high. The most marked change is in the finger tip. Regeneration is practically never complete, except in some of the earlier cases denervated by ramisectomy and trunk section.

Because of the uniformly gratifying immediate and early results,¹⁰ and because equally satisfactory late-results have been obtained, it seems desirable to persist in the attempt to prevent and further minimize regeneration which is the principal cause of inferior late-results. It is perhaps not too much to

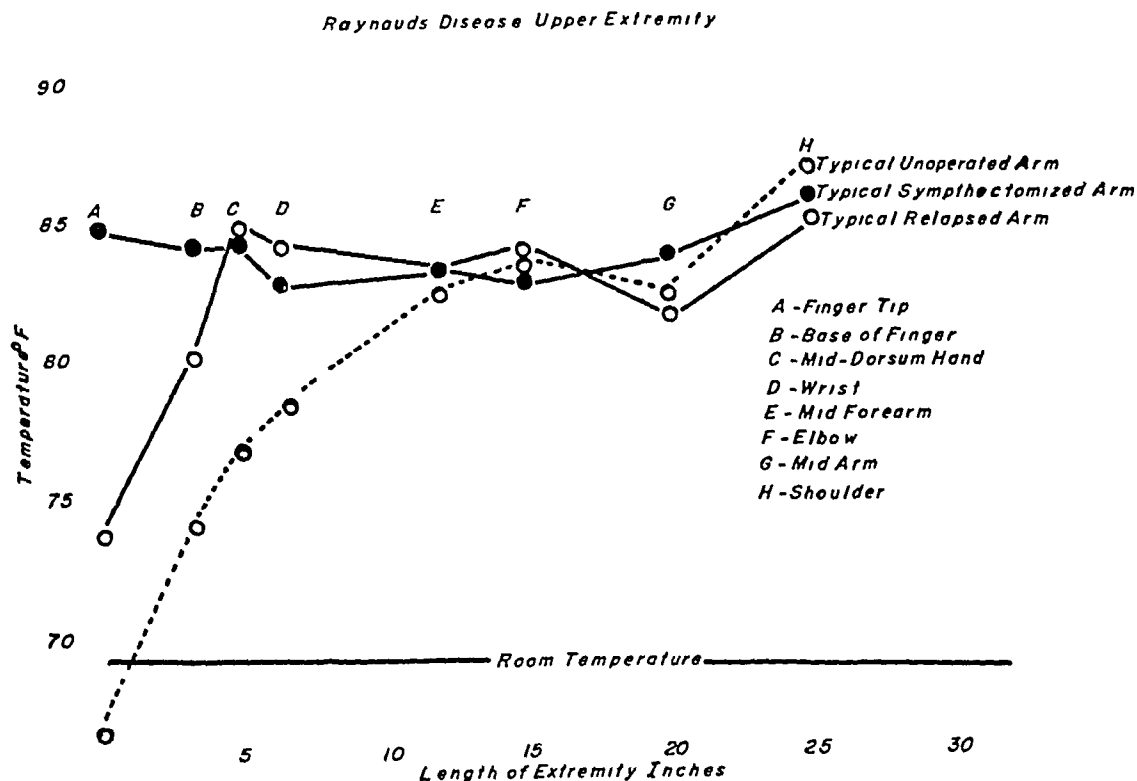


FIG 14—When the vasospastic upper extremity is exposed to a cool environment, and surface temperatures are recorded at frequent intervals from the finger tip to the shoulder a characteristic curve results. The temperature is well sustained from the shoulder to the upper third of the forearm. It then falls abruptly, so that the finger tip is generally below the room temperature. When sympathectomy is complete a high surface temperature is found. Almost the same level is maintained from finger tip to shoulder, except when marked organic disease exists before operation. When regeneration of moderate to marked degree is found, the surface temperatures are sustained from shoulder to midhand. From there distally, cooling is noted to be most marked at the finger tip. This usually, however, still remains above room temperature and the relapsed extremity resembles a normal extremity examined under the same circumstances. These findings are in accord with the late clinical results which are beneficial to the patient even if definite evidence of regeneration can be demonstrated. The latter is rarely complete.

expect that this difficulty either may have been or can be solved without increasing the magnitude or risk of the operation.

CONCLUSIONS

(1) The upper extremity can be thoroughly sympathectomized by interrupting the outflow from the second and third dorsal segments and dividing the sympathetic trunk below its third ganglion. The outflow from D1 is not important in man.

(2) The immediate results are uniformly satisfactory. The late-results are variable. This is due to cooling of the extremity, which in most instances is caused by regeneration of sympathetic motor nerves.

(3) A number of variations in surgical technic are discussed. These changes have been made primarily to guard against regeneration.

(4) Even in the presence of a considerable degree of regeneration, the blood flow to the extremity is improved, and the result worth while from the patient's point of view. Regeneration is rarely complete.

(5) It seems reasonable to expect that further precautions which have or can be taken against regeneration will make the late-results even more satisfactory.

REFERENCES

- ¹ Freeman, N. E., Smithwick, R. H., and White, J. C. Adrenal Secretion in Man. *Am Jour Physiol*, 3, 107, 1934.
- ² Smithwick, R. H., White, J. C., and Freeman, N. E. Effect of Epinephrine on the Sympathectomized Human Extremity. *Arch Surg*, 29, 759, 1934.
- ³ Langley, J. N. On the Origin from the Spinal Cord of the Cervical and Upper Thoracic Sympathetic Fibers, with Some Observations on White and Grey Rami Communicantes. *Phil Trans Roy Soc, London, S B* 183, 85, 1892.
- ⁴ Kuntz, A., Alexander, W. F., and Furcolo, C. L. Role of Preganglionic Fibers of First Thoracic Nerve in Sympathetic Innervation of Upper Extremity. *Proc Soc Exper Biol and Med*, 37, 282-283, November, 1937.
- ⁵ Smithwick, R. H. Modified Dorsal Sympathectomy for Vascular Spasm (Raynaud's Disease) of the Upper Extremity. *ANNALS OF SURGERY*, 104, 339, September, 1936.
- ⁶ Telford, E. D. The Technique of Sympathectomy. *Brit Jour Surg*, 23, No 90, 448, 1935.
- ⁷ Simmons, H. T., and Sheehan, D. An Inquiry into "Relapse" Following Sympathectomy. *Lancet* 2, 778, October, 1937.
- ⁸ Simmons, H. T. and Sheehan, D. The Causes of Relapse Following Sympathectomy on the Arm. *Brit Jour Surg*, 27, No 106, 234, 1939.
- ⁹ Page, I. H. Personal communication.
- ¹⁰ Smithwick, R. H. Surgical Intervention on the Sympathetic Nervous System for Peripheral Vascular Disease. *Arch Surg*, 40, 286-306, 1940.

DISCUSSION—DR. PETER HLINBECKER (St. Louis, Mo.) We envy the richness of Doctor Smithwick's experience. Mere volume of work, in itself, would not be significant in this field. His contributions to the body of knowledge governing the treatment of spastic vascular disease have contained many significant physiologic observations. We hope that he will not take amiss the temerity which leads us to differ with certain of his concepts. Concepts determine the course of modifications in treatment.

Spastic vascular disease is regarded by Lewis and coworkers as a primary disease of the blood vessel musculature. In this we concur, and we believe that evidence has been furnished by us to show that the blood vessels of individuals so afflicted respond hyperdynamically to nervous and to humoral influences. The disease may, in itself, be progressive but, ordinarily, its progress is modified by such influences. It is not believed that the disease is due to a primary hyperfunction of vasomotor nerve centers. It is easily understood, then, that we are loath to interpret progression of the disease, after a proper sympathectomy, as due to regeneration of autonomic nerve fibers. The criterion for such regeneration is often the supposed return of varying degrees of sweat gland function. Is it certain that the tests employed do not yield a positive result from the secretion of sebaceous glands and from the loss of insensible perspiration? Doctor Smithwick has secured evidence of a

rise in temperature of the fifth finger, after appropriate nerve blocking. This could be interpreted as the result of an incomplete denervation (D1 interruption omitted), which makes itself manifest after sensitization from partial denervation has had time to develop instead of considering it an expression of sympathetic nerve fiber regeneration.

Sympathetic nerve fiber regeneration following postganglionic denervation (removal of ganglia) could at its maximum be trifling. The ratio of pre- to postganglionic fibers in regions where it has been investigated has been found to be about 1 to 30. If, then, all preganglionic fibers could be supposed to find their way to an end-organ, the effect could not be more than one-thirtieth of the normal. Direct action of regenerated preganglionic neurons on effector organs has never been demonstrated. In the preganglionic type of denervation some of the fibers, possibly, could connect again with postganglionic neurons and in this way exert a greater influence. All our clinical reports indicate that preganglionic denervation results in fewer signs of regeneration than does postganglionic denervation. There is no *a priori* reason why regeneration should not occur, also, following lower extremity ganglionectomy with equal facility as in upper extremity operations. No one will deny that the end-results of lower extremity operations are very much better than those following upper extremity operations. The explanation, therefore, probably does not reside in the regeneration factor at all. To add further difficulty to the theory of regeneration when needed to explain a return of sweating, it might be stated that the investigation of André Thomas led him to the conclusion that the arm and upper chest segments derived their nerve supply for sweat glands from D5 to D7. In most operations now performed, the sympathetic trunk is cut below D3 and elevated several inches in the wound. This would certainly make regeneration from levels D5 to D7 a hazardous adventure.

It is the belief in our clinic that the upper extremity is not denervated completely unless the sympathetic fibers from D1 are eliminated. Man's organization is a modified metameric one. It seems likely, then, that sympathetic fibers from a particular root level would at least supply that level no matter what other levels it might supply. Our belief is based also on the excellent anatomic studies by Albert Kountz in the dog and in the cat in which he has shown that as much as 50 per cent of the sympathetic outflow to the arm may come from D1. The burden of proof would appear to rest on anyone accepting the idea that man differs materially from these animals in his nerve fiber distribution.

It is granted that preganglionic denervation is preferable to postganglionic denervation because the sensitization to epinephrine of the blood vessels, denervated preganglionically, is less.

It has been shown, recently, by Homer Smith, that in the prone position the circulation of the kidney functionally denervated by spinal anesthesia is not increased over the normal. As soon as the upright position is assumed, vasoconstrictor influences become effective in cutting down the renal blood flow. This indicates that in the upright position vasoconstrictor influences exerted on the blood vessels of the lower extremity are most active. It seems reasonable to assume that such vasoconstrictor influences, whose measure is dependent upon posture, would be much greater in the lower than in the upper extremities. Hertzmann, of St. Louis, has found that, in the semireclining position, the blood flow through the toes is always less than in the fingers. To the extent that this is due to nervous influences denervation of the lower extremities would then eliminate vasoconstrictor influences of greater magnitude than in the upper extremity. In this resides, in our opinion, the main

reason for the better clinical results of operations on the lower extremity than on the upper in cases of spastic vascular disease

DR JAMES C. WHITE (Boston, Mass.) I think that this work depends so much on underlying animal physiology that it should be worth while to spend just a moment to review the experiments upon which it was based. We know the modern physiologic concept that nerve impulses are conducted electrically over the nerve, but that a chemical substance propagates the discharge from the nerve ending to the muscle fibers. Furthermore, when the nerve fiber degenerates, the action of the chemical substance on the denervated neuro-effector mechanism becomes greatly intensified. This principle of sensitization applies not only to the sympathetic system, where adrenalin and sympathin are the chemical factors, but also to the parasympathetic, where acetylcholine is the chemical mediator.

The best way to show how important this is is to take a monkey and denervate his arm by cutting all the anterior thoracic nerve roots from the second down to about the tenth. Those are the ones that give off the vasoconstrictor impulses. You do not have to cut the first. Having done that, follow the skin temperature of the fingers as the monkey becomes excited or as he reacts to a small dose of adrenalin. His hands cool off very little. Then take that monkey and resect the inferior cervical and first and second thoracic ganglia on the same side. His hand will then cool markedly as soon as he gets excited or is injected with adrenalin. Peter Ashcroft, working in Doctor Fulton's laboratory in New Haven, has shown the same phenomenon in the lower extremity.

Now, in the second place, about the tendency of these structures to regenerate. Here again, animal work has a great deal to show. Dr Ferdinand Lee, at Johns Hopkins, pointed out that when the cervical sympathetic chain is cut and the two ends placed on opposite sides of the sternomastoid, the pupillary reactions return within a period of four weeks, and in serial sections through the muscle, regenerating axones can be followed across the gap.

An effective sympathectomy, in addition to eliminating the possibility of regeneration, must cut all the nerve fibers to a given area. Recent work, in Doctor Cannon's laboratory by Doctor Simeone, has shown that even if you destroy 90 per cent of the innervation of the smooth muscle, the remaining 10 per cent of the fibers, by secreting sympathin at their endings, can fire off the paralyzed portion of the muscle. So your operation must not only prevent regeneration but it must be a complete sympathectomy in addition.

In the third place, it does not seem fair to apply finer physiologic points from animals to man. That is particularly true in neurology, and just because you can show vasoconstrictor fibers to the arm in the first thoracic nerve of the cat or dog does not necessarily prove their presence in human beings. So far as I know Doctor Heinbecker and Doctor Kuntz have no evidence to show that the first thoracic nerve carries important vasoconstrictor or sudomotor fibers to the arm in man.

There are a great many new tests which have been put into general use for testing regeneration—determination of electrical skin resistance in ohms, measurements of the minute vasoconstriction that can be observed with the finger plethysmograph. When postoperative patients are followed in this way, one can really determine when regeneration has taken place, but, so far, these tests have not been in general use in other clinics.

Because of the extraordinary tendency of the preganglionic fibers to regenerate this new operation for Raynaud's disease has been fraught with great difficulty. I think Doctor Smithwick deserves extraordinary credit for over-

coming these difficulties, and it is really fair to say that at the end of a year, or even two years, after preganglionic denervation of the upper, as well as the lower extremities, many of the hands of his patients are just as warm as the feet

DR MAX M PEET (Ann Arbor, Mich) I feel that those of us who are performing neurosurgery owe a big debt of gratitude to Doctor Smithwick and Doctor White for the work that they have been doing, particularly to point out the difference in the final action between pre- and postganglionic sympathectomy At our various neurologic surgical meetings we frequently argued as to why we obtained such good results in the lower extremities by lumbar sympathectomy and almost uniformly got poorer results in the upper The latter patient is improved, but on exposure to cold and particularly under excitement or mental stress, there develops a certain amount of vasoconstriction I think it rarely tended to the point of gangrene in the finger tips, but it was rather common that vascular constriction would be sufficient to cause blanching of the fingers and many times pain

So, when Smithwick first brought out this idea, really originating, of course, in Cannon's laboratory, that the preganglionic section did not make those blood vessels particularly sensitive to circulating adrenalin and sympathin, we immediately took up that approach ourselves I visited Doctor Smithwick, watched him operate, and talked it over in detail We have been following his technic since I realize that there is probably no part of the nervous system that regenerates as readily as does the sympathetic The fifth nerve, peripheral to the gasserian ganglion, is possibly an exception, but we have overcome this difficulty by section of the nerve central to its ganglion

As to how we are going to overcome these regeneration tendencies of the sympathetic nerves I am not certain, but they do not always regenerate, and we have had some cases that have apparently remained permanently cured There is no question, in my mind, that the first thoracic nerve does not supply sympathetic fibers to the arm We have tested many of these patients by the sweating test, and there has been no evidence whatever that sympathetic fibers to the arm come off with the first thoracic There is much evidence that the fibers do come off the second, third, and even down as low as the twelfth thoracic

We have had patients who developed Raynaud's disease from a proven lesion in the brain This I think proves, quite conclusively, that this may be a disease of central origin and not a local disease of the blood vessel True, after Raynaud's disease has advanced sufficiently you do get local disease in the peripheral vessels, but as a primary disease I think it is one of the central nervous system The object of the whole operation is to break the connection between the central nervous system, or at least the spinal cord, and the peripheral vessels Doctor Smithwick's procedure has been very efficient except for the tendency to regeneration I think perhaps he has overcome that

DR REGINALD H SMITHWICK (Boston, Mass) I dislike to bring up at this time, the question of the etiology of this disease because ever since Raynaud described it in 1860, it has been a very fruitful subject for argument and, apparently, still is, and perhaps in our present state of ignorance it is less important to know the etiology of the disease than to be able to select cases in which you can prove beforehand that something really worth while can be accomplished for the patient Of course time did not permit me to speak of the type of cases in which this operation was performed but over two-thirds of them had considerable evidence of local fault as described by Sir Thomas

Lewis, either as the result of long-standing vascular spasm, or because the vascular spasm was known to be secondary to some organic disease of the vessel, such as sudden occlusion of major arteries, thrombo-angitis obliterans, arteriosclerosis, and various other lesions. I can say that, providing regeneration is prevented, these patients with definite organic changes have obtained some of the best results in the series, and I disagree with those who would limit the field of application of such a procedure to only the very earliest cases without evidence of organic change.

Time, of course, did not permit me to summarize our evidence for the fact that *Dr* is not of importance in man. Doctor White and Doctor Heinbecker have pointed out that the evidence on which the supposition that *Dr* is of importance, comes largely from animals. While one can draw conclusions from animals to man in certain regards, it certainly is very dangerous to do so as far as anatomy is concerned. The evidence which we have on this point was presented in detail a year ago here in St. Louis and published early this year.

I regret to bring up the matter of the lower extremity because it really has not much to do with the upper extremity, as far as this discussion goes, but I can say that we have almost as many cases that have regenerated in the lower extremity as we have in the upper extremity and that regeneration there is a very important problem. Even though one can undertake a much more radical procedure from the point of view of separation of the divided ends of the trunk in the lumbar region than in the dorsal region, nevertheless, as we follow our late cases four, five, six, eight, ten years after operation and check on them very carefully, we realize that a very high percentage of them have significant evidence of regeneration.

To my mind, we have passed the point where it is a question of knowing what to do in order to denervate either the arm or the leg. We understand that well, and obtain many good, lasting, worthwhile results. The chief problem to-day is to prevent regeneration and, as far as I know, nobody has ever found a way to do that as yet.

A RÔLE FOR SURGEONS IN THE PROBLEM OF ESSENTIAL HYPERTENSION*

PETER HEINBECKER, M D

ST LOUIS, MO

FROM THE DEPARTMENT OF SURGERY, WASHINGTON UNIVERSITY, AND THE BARNES HOSPITAL ST LOUIS, MO

CONFLICTING EVALUATIONS of the result of splanchnic section for essential hypertension are being made. In spite of the enthusiasm of the surgeon, the internist has not been convinced of its efficacy. The availability in this field of follow-up results of longer duration (Craig and Adson 1939, Peet, 1939, Heinbecker, unpublished data), together with a better understanding of the pathologic physiology of hypertension, makes possible this analysis in which an attempt will be made to outline a rôle for surgeons dealing with the problem of essential hypertension in man. In a subject of such rapid development as our knowledge of the control of blood pressure, one must face the possibility of reading with a sense of embarrassment at some later date what one now writes with full confidence. The outlook for the discovery of a substance to neutralize the action of agents known to decrease the caliber of blood vessels in the state of hypertension in man is not too fanciful to be entertained.

FACTORS IN NORMAL BLOOD PRESSURE CONTROL

Blood pressure is determined by the cardiac output and the peripheral resistance of the vascular tree. The latter is dependent, primarily, upon the caliber of the terminal arterioles. These possess an inherent tone which is subject to modifications by nervous and by humoral influences.

Rôle of the Nervous System—The nervous control of the size of blood vessels is one of the most essential regulatory systems in the body. Special moderator sense organs located in the walls of the aorta, the carotid sinuses, in the mesentery and, possibly, throughout the blood vessels of the body respond to variations in pressure within the vessels by discharging impulses whose frequency closely follows fluctuations of arterial pressure. These impulses are transmitted to the cardiovascular medullary centers, and from these centers over the sympathetic and parasympathetic nerves a stream of impulses modifies the tone and thereby the caliber of the blood vessels. They modify, also, the rate and force of the heart beat. A rise in pressure results in a decrease of the vasoconstrictor impulses, a slowing of the heart and an increase of vasodilator influences. A fall in pressure results in an increase in vasoconstrictor impulses, a decrease of vagal inhibition of the heart and a diminution of vasodilator impulses. The circulation in the normal individual is thus largely self-controlled.

* Presented by title before the American Surgical Association, St Louis, Mo., May 1, 2, 3, 1940.

It is believed by Smith (1939) that under basal resting conditions the normal renal blood flow in man is not tonically affected by nervous influences. In the upright position reflex vasoconstrictor influences narrow the afferent arterioles of the kidney appreciably as shown by a decrease in renal plasma flow at a time when the mean arterial pressure is not decreased. There is a concomitant fall in the filtration fraction, indicating that the constriction is in the afferent rather than in the efferent arterioles.

Rôle of the Endocrines—The degree to which the caliber of the blood vessels is normally modified by the secretions of the endocrine glands is less definitely known. Loss of the adrenal glands, especially their cortical division, is associated with generalized hypotonicity of all body musculature and with hypotension. The inference seems justified that these hormones normally aid in maintaining blood vessel tone. Pituitary hormones may also play a role because total hypophysectomy tends to lower blood pressure somewhat (White and Heinbecker, unpublished data). This may, however, in whole or in part, be a consequence of a diminished cardiac output because White and Heinbecker (1940) have shown that at certain periods following hypophysectomy the diodrast plasma clearance and, therefore, presumably the renal blood flow are diminished as much as 50 per cent.

Rôle of the Kidney—The recent demonstration that the ischemic kidney releases a pressor substance (Harrison, Blalock, Mason and Williams, 1936) suggests that the normal kidney may have, within itself, the mechanism for the secretion of humoral substances which can insure the normality of its own blood flow by modifying the caliber of the blood vessels of the kidney and the body generally. The actual status of this mechanism in the control of blood pressure in the normal individual remains to be established.

BLOOD PRESSURE IN HYPERTENSION

The blood pressure changes in essential hypertension are characterized by a rise in both diastolic and systolic pressures. In order that the diagnosis be made, the diastolic pressure must be raised. There is general agreement that some measure of hypertension exists when the diastolic pressure is 100 Mm Hg or over. This is effected by a generalized vasoconstriction as it has been amply demonstrated that cardiac output (stroke volume \times heart rate) is not modified in essential hypertension. Other factors such as blood volume and blood viscosity are also normal.

The State of the Arteries in Hypertension—The assumption is too often made that the vascular musculature of all persons has identical physiologic properties. Evidence, much of which, it is true, cannot be easily subjected to rigid experimental tests, is nevertheless, at hand to suggest that the responsiveness of vascular smooth musculature to nervous and humoral influences may vary quantitatively if not qualitatively in different individuals. The basis for such variations in responsiveness is regarded as genetic or constitutional and its nature is not known. This concept is supported by the evidence of a marked difference in the circulatory response of different in-

dividuals on exposure to cold (Hines and Brown, 1933) and to exogenous epinephrine (Jensen, 1930). It is also supported by the evidence that in persons exhibiting the Raynaud syndrome (Heinbecker and Bishop, 1938) the blood vessels respond hyperdynamically to nervous and to humoral influences when compared with other individuals.

On the other hand, there is evidence that environmental factors are required to bring out a constitutional predisposition to hypertension. Thus, African Negroes of similar strain to the imported North American Negroes have little or no hypertension while in America Negroes have hypertension in increasing degrees (Domison, 1929, and Allen, 1931). This can be interpreted as indicating that certain of the imported individuals were of the type possessing blood vessels with an inherent tendency to respond hyperdynamically to vasopressor influences, these individuals, when placed under environmental circumstances which increased such influences, developed hypertension. Statistics reveal that persons, one or both of whose parents had essential hypertension, have a much greater tendency to develop hypertension than do persons neither of whose parents had hypertension (Weitz, 1926). The inference must not be made that this is an instance of the inheritance of acquired characteristics, as geneticists deny the possibility. What is inherited is the degree of responsiveness of their blood vessel musculature to vasopressor influences. In the author's opinion an analysis of those environmental factors known to modify blood pressure and which the American Negro, especially the city dweller, is subjected to in greater degree than the African Negro leads to the impression that the most important ones act through the nervous system. Such nervous influences could narrow the blood vessel caliber directly, or indirectly, through humoral influences. Hypertension could presumably result if such action brought about constriction of the renal vessels.

Neurogenic Factors in Essential Hypertension—The impression that neurogenic factors are in themselves always responsible for the generalized vasoconstriction of essential hypertension can no longer be entertained. This is evident from the failure of extensive sympathectomy in humans to lower the blood pressure at a time when generalized and renal arterial degeneration is not marked. That they may, however, play a rôle is evident from those case reports in which a definite and sustained drop in diastolic pressure has followed splanchnic section. That other factors can bring about hypertension is shown by the reports of cases in which the blood pressure has risen following a temporary lowering from splanchnic section where nerve regeneration can be excluded. Experimental evidence that hypertension of renal origin can be effected through nervous influences has been afforded by Heymans and his associates, in dogs (Gimson, Bouckaert and Heymans, 1939). These investigators produced a prolonged rise in blood pressure in animals in which sympathectomy, except for the nerves to the kidneys and adrenals, was complete and in which the moderator nerves from the carotid arteries and the aorta were removed. No hypertension developed in animals so

treated with the moderator nerves intact. The hypertension was eliminated when the nerve supply to the kidneys was removed. Their results demonstrate that the kidney can play an essential rôle in the development of hypertension and that a nervous mechanism can initiate the process in the kidney which leads to hypertension.

No cogent evidence exists to indicate that a defect in function of the moderator mechanism is the cause of hypertension in man. Gannon (1936), Pickering, Kissin and Rothschild (1936) have shown that in persons with hypertension, pressure on the carotid sinus produces as much slowing of the pulse and drop in blood pressure as in normal individuals. It is true, however, in the large majority of cases of essential hypertension that there is an absence of bradycardia during sudden rises of blood pressure. At present the mechanism for this remains unclear.

There remains the possibility that the action of the central nervous system, especially of the diencephalon, in initiating vasoconstrictor impulses is exaggerated in its response to the extrinsic and intrinsic stimuli reaching it under the conditions of man's existence in modern civilization (Raab, 1931). More evidence is desirable before the acceptance of this hypothesis.

Endocrine Factors in Hypertension—Normally, under basal conditions the caliber of peripheral arterioles is not known to be greatly modified by the products of the endocrine glands except in the case of the adrenal cortex. The presence of an excess amount of epinephrine or of adrenal cortical hormone such as is found in the presence of tumors of these structures may result in hypertension of the essential type which is completely relieved by removal of the tumor.

Cushing's (1932) description of pituitary basophilism has pointed to a possible constrictor rôle of one of the pituitary hormones when present in an excess amount but, so far, no proof of the existence of such a hormone has been presented. It is suspected by some that the effect may be an indirect one through the adrenal cortex. It seems probable that the action of the hormones of the adrenal and of the pituitary gland in the mechanism of human hypertension is synergistic with that of a pressor substance from the kidney.

The Rôle of the Kidney in Hypertension—From the very beginning of our attention to blood pressure, clinical studies have indicated that the kidney may play an important rôle in hypertension. There has been controversy about whether the renal pathology is primary or secondary. The recent work of Goldblatt and his associates (1934, and subsequent papers) appears to have answered this question in their demonstration that renal ischemia leads not only to hypertension but also to occlusive disease of the blood vessels of those organs of the body in which pathologic studies on human cases of essential hypertension have shown such lesions to exist. That such lesions could not be expected to be present in the kidney under Goldblatt's experimental conditions is obvious because in that organ the blood pressure is low due to the clamp placed on the renal artery. This, in itself, seems good evidence that the continued hypertension has led to the occlusive disease in the other arteries. The

mechanism of the development of hypertension by the ischemic kidney has been investigated by Goldblatt (1934, *loc cit*) by Page and Hilmer (1940) and others. An analysis of their results indicates that the ischemic kidney releases a pressor substance such as was designated "renin" by Tigerstedt and Bergman (1898). This leads to the production of a generalized vasoconstriction. Admittedly, there are many who do not consider it proven that in human essential hypertension this is the mechanism of the hypertension. There is no established mechanism to account for the initiation of the renal ischemia. The lack of an explanation of its origin does not invalidate the excellent physiologic evidence that such ischemia is possible. The studies of Smith (1939, *loc cit*) and of Findley and White (unpublished data) show that in patients with early hypertensive disease, before clinical evidence of renal damage is obvious, there is, nevertheless, a diminished renal blood flow. Smith finds that the diminution in tubular function is sometimes less than is the diminution in blood flow. This suggests that the diminution of vascular function is primary in time and that the disturbance in tubular function is the result rather than the cause of renal ischemia. The results of these workers further indicate that the immediate disturbance of function is a constriction of the efferent glomerular arteries. This is similar to the effect on the kidney vessels produced by epinephrine and by renin (Corcoran and Page, 1939).

That the Goldblatt principle plays a primary rôle in some forms of human hypertension is definitely shown by the demonstration that all signs of the disease are in some instances obliterated by removal of a single diseased kidney (Barker and Walters, 1938). A basis for an impairment of the renal blood flow exists in other forms of renal disease associated with hypertension—in inflammatory diseases of the kidney, in the vascular changes of old age, and in the obstructive lesions of the lower urinary tract where pressure changes in the kidney would be expected to be reflected on the renal blood vessels.

The demonstration that relief from renal ischemia will result in the elimination of all signs of the disease in man would incriminate the kidney as a primary factor in hypertension beyond any doubt. One way in which this might be accomplished is by renal denervation. If such a result followed, it would answer the question as to whether or not nervous influences are responsible for the initial vasoconstriction of the kidney vessels. While it is the author's opinion, based on clinical observations, that such influences will be found responsible for the initial vasoconstriction in many cases, it is felt probable that in other cases humoral influences will be found to play that rôle. The possibility also exists that hypertension follows from a disease process which is primary in blood vessels, particularly the renal blood vessels, of a type in which functional narrowing is a first manifestation, with later spontaneous progression to an occlusive stage. This seems to be the course of events in certain cases of spastic vascular disease of the extremities (Heimbecker and Bishop, 1938, *loc cit*). Here, nervous and humoral influences merely modify the rate of progression of the disease process which may never become of clinical significance without them. Such a disease process may be based on a constitutional tend-

ency of the blood vessels of certain individuals to respond hyperdynamically to normal nervous or humoral influences. Any excess of such influences over the normal would exaggerate the blood vessel constriction. Such functional constriction would doubtlessly involve the vasa vasorum and might, thereby, lead to degenerative changes in the intimal and subintimal layers by interference with their blood supply. Evidence in support of such a hypothesis has been furnished recently by Wintemitz, Thomas and LeCompte (1938) in their discussion of the biology of arteriosclerosis.

Synergistic Action of a Renal Substance and Epinephrine—From an analysis of our end-results of splanchnic section in humans, it was evident that symptomatic relief from headache, from a sense of cardiac oppression and from restlessness was obtained in cases in which there was no lowering of the blood pressure. Inasmuch as the operation denervates the adrenals as well as the kidneys, it was suspected that the adrenal denervation might be responsible for such relief in persons with hypertension. It was known that adrenal denervation lowers the amount of circulating epinephrine. No direct evidence of the effect of this on the properties of nerve elements in the body was available. However, a depression of nervous reactions by extensive sympathectomy in otherwise normal animals has been demonstrated by Hines and Brown (1933, *loc cit*). It seems reasonable to assume that this depression resulted from the adrenal denervation. A similar result should follow in man. The fact that in a high percentage of cases in persons with hypertension the reaction to cold is exaggerated, as it also is to intravenous exogenous epinephrine, led to the suspicion that in such persons the mechanism leading to hypertension might increase coincidentally the effect of epinephrine on their smooth musculature.

Experimental Evidence—To investigate this problem cats were used as experimental animals. One superior cervical sympathetic ganglion was removed to sensitize the pupil to epinephrine. After recovery from this operation the horizontal diameter of the cats' pupils was measured in a darkened room under standard lighting conditions. The measurements were made when the cats faced a 300 watt electric light bulb at a distance of two meters. After training, it was possible to get consistent readings after a preliminary rest period of 15 minutes. The smallest diameters of the left and right pupils which could be obtained and the degree of retraction of the nictitating membranes were noted. Then 0.3 to 0.5 cc of epinephrine 1:1,000 (Burroughs and Wellcome) in 5 cc of a physiologic saline solution was injected intraperitoneally and the size of the pupils measured at intervals of ten minutes, until they returned to the original or preinjection sizes. This usually occurred after 30 minutes. The same procedure was repeated two or three times with an interval of four or five days between observations. The results of the tests were strikingly uniform.

With this dosage of epinephrine there was usually no change in the size of the normal pupil, the sympathectomized pupil generally enlarged 0.5 to 1

Mm The normal mictating membrane usually was unaffected while the sensitized one showed slight retraction

In 19 animals, in which one or both renal arteries were constricted by the method of Goldblatt, five showed a definite and lasting increase in the diameter

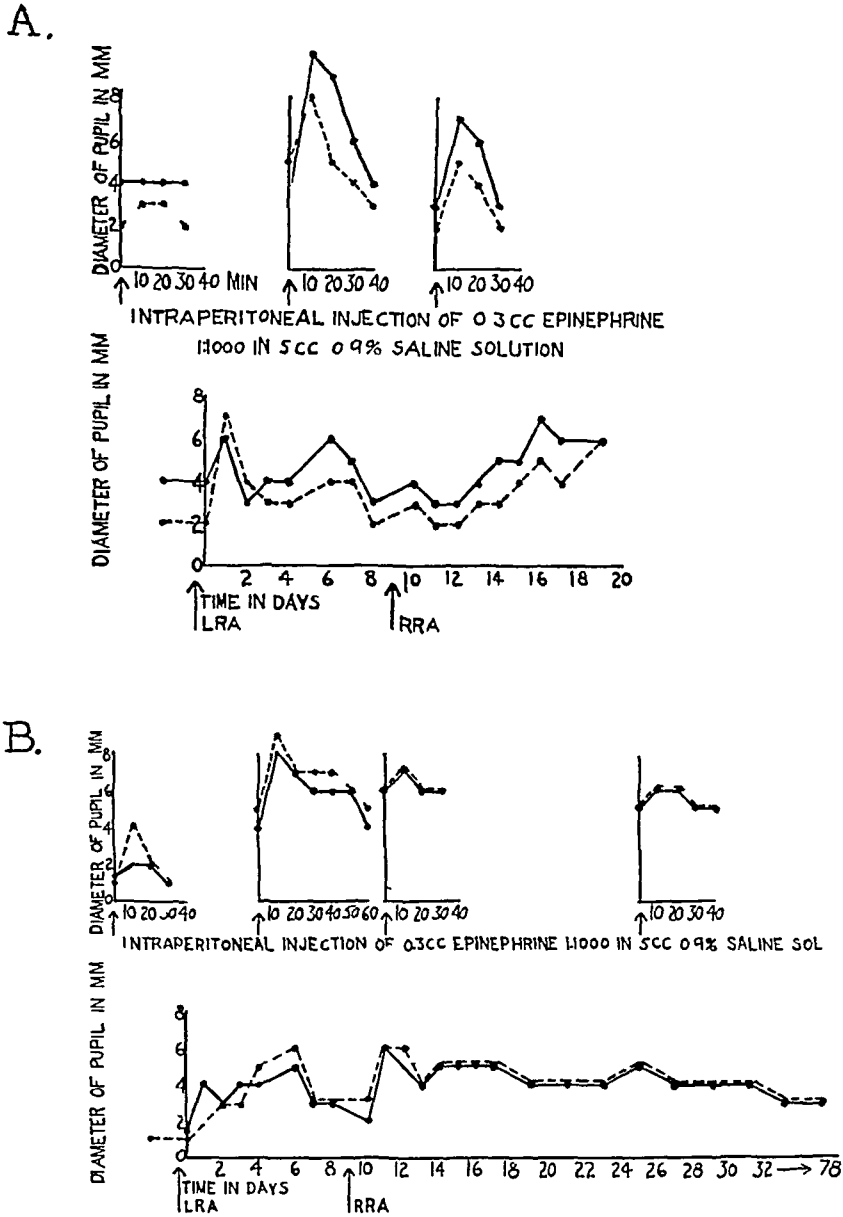


CHART 1—Graphs A and B show the responsiveness of the pupils of two cats to exogenous epinephrine 0.3 cc in 5 cc N/saline given intraperitoneally and their transverse papillary diameters at various intervals after the application of Goldblatt clamps to their renal arteries. LRA and RRA indicate times of application of clamps to left and right renal arteries respectively. Broken line for sympathectomized pupil, solid line for companion pupil.

of both pupils, the sympathectomized ones showing a relatively greater increase (Chart 1). In fact, in three of the cats the sympathectomized pupil became equal in size to the normal. In five other animals a transient increase in the sizes of both pupils was obtained. The remaining animals, some of which did not live more than a week, showed no change. In all instances, where a definite increase in the size of the pupil was secured, there was also an

increase in their responsiveness as evidenced by pupillary dilation to exogenous epinephrine. In four other cats, in which one kidney was removed and the other wrapped in silk, according to the method of Page (1939), there was a gradual increase in the size of the sympathectomized pupil and a moderate increase in response of this pupil to exogenous epinephrine. In one of the cats the sympathectomized pupil became larger than its companion pupil which also increased somewhat in size (Fig 1). Both pupils in this animal were greatly sensitized to exogenous epinephrine. In general, it seems true that the degree of increased responsiveness to epinephrine goes hand in hand with the degree of increase in size of the pupil. The tone of the denervated nictitating membrane as evidenced by its retraction was increased following renal ischemia in over 60 per cent of the animals. It is not possible to judge accurately the tone of the companion nictitating membrane.

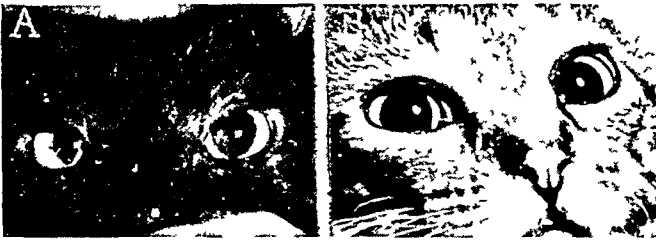


FIG 1.—Photographs showing the pupils of two cats. A Normal cat one week after removal of right superior sympathetic ganglion. B Another cat three months after removal of right superior sympathetic ganglion, removal of one kidney and envelopment of other kidney in silk. Note in A right pupil smaller than left, in B right pupil actually larger than left.

It is realized that these experiments are incomplete in that no blood pressure readings are available. In chronic animals autopsy, however, revealed definite left ventricular hypertrophy which may be regarded as fair evidence of the existence of previous hypertension. Such animals had a moderate elevation of urea nitrogen (50 to 90 mg %) but there was no correlation between the degree of nitrogen retention and the degree of change in the size or responsiveness of the pupils. It is to be noted that the removal of all renal tissue in the normal or hypertensive cat will, after two days, in itself, sometimes result in an enlargement of the sensitized pupil and in an increase in its responsiveness to exogenous epinephrine. It seems reasonable to consider on the basis of our experiments that the substance released from the ischemic kidney which increases the tone of the smooth musculature of the eye of an animal and makes it more responsive to epinephrine is also the pressor substance. Verney and Vogt (1938) report that in three out of seven hypertensive dogs there was a marked increase in their sensibility to epinephrine when blood pressure response was used as a criterion.

Our results are taken to indicate that in certain cats renal ischemia may lead to an increase in the tone of the smooth musculature of other structures as well as blood vessels. This effect on the eye musculature and possibly also on the blood vessels may result in a coincidental increase in their responsive-

ness to exogenous epinephrine. This is not construed as indicating that in certain animals hypertension is due to a sympathomimetic substance like epinephrine though epinephrine may play a rôle, for instance, in the hypertensive crises in cases of human hypertension. It also affords a basis for the belief that adrenal denervation in certain individuals may have a very definite influence on their nervous reactions.

The failure to get positive results in all animals is not explained. It is possible that an inadequate degree of renal ischemia was produced in some or it may be that animals like humans differ in their reactivity to stimuli affecting their smooth musculature.

Effect of Epinephrine and Adrenal Denervation on the Nervous System —

The effect of epinephrine on the isolated, spontaneously active ganglion cells of the *Limulus* heart cord is to increase the frequency and the magnitude of the ganglion cell response (Heinbecker, 1936). In experiments now in progress, the effect of an increase in the amount of circulating epinephrine on the activity of the central nervous system of the cat is being determined. Preliminary results demonstrate that such an increase of epinephrine results in a lowering of the threshold for the immediate cortical response to saphenous nerve stimulation and causes an augmentation in the size of this response to stimuli of a given strength. An increase in the general cortical activity is evidenced by an increase in the size of the cortical potentials.

During activity, the central nervous system must be influenced by the circulating epinephrine. In view of the results cited, it seems reasonable to assume that a diminution in the amount of circulating epinephrine, such as would be effected through adrenal denervation, would raise the threshold for the cortical response to afferent stimuli and diminish the size of the response to stimuli of a given value. Such effects would seem to afford a possible explanation of the raised threshold for discomfort and the lessened excitability of persons with hypertension on whom a splanchnic section has been carried out.

Clinical Effects of Splanchnic Nerve Section — From our knowledge of the mechanism of the production of hypertension and of the associated effects in animals, certain inferences can be drawn as to what could be expected from splanchnic section in various stages of the disease in humans. Four case records to illustrate the actual results for comparison with those theoretically expected are presented.

Consider, first, the stage where the renal ischemia is brought about by functional narrowing of the renal vessels through nervous influences with no irreversible kidney damage. Splanchnic section should permit the renal blood flow to return to normal, the hypertension should be completely relieved. Such a stage is believed to be illustrated in Case Record 1.

Case Record 1 — I. D., white, female, age 20. Elevated blood pressure discovered during routine examination—only symptom, slight dyspnea on exertion. Father died of heart disease; mother living, has hypertension. Two brothers and one sister have hypertension. Blood pressure 180 to 160/110 to 105. Eyegrounds normal. Urea clearance 76 per cent. Urine normal. Heart not enlarged. After nembutal, blood pressure

130/90 In cold pressor test, blood pressure rose from 155/105 to 180/120 Bilateral splanchnic section, April, 1938 After operation, blood pressure dropped to 120/60 and remained there for eight months Was married, January, 1939 Miscarriage after three months' pregnancy, August, 1939 In November, 1939, blood pressure 144/98, in March, 1940, blood pressure 165/110 Patient has slight dyspnea, is nervous and somewhat irritable

Case Record 1 further demonstrates the detrimental influence of pregnancy on a patient with potentialities for the development of hypertension Humoral influences released during pregnancy presumably again produced narrowing of the denervated renal vessels of the kidneys, and thereby initiated a disease process which, in our experience, is progressive, when not relieved by parturition It illustrates a mechanism for the production of hypertension unassociated with the nervous control of the kidneys Such a mechanism does not require the autonomic nervous system even for its initiation Splanchnic section could not be expected to have any great influence on its progress

Consider, next, a stage in which renal ischemia initiated through nervous influences has been present for some time and where the narrowing of the renal vessels is now held to be due to a self-perpetuating renal pressor substance Damage to the renal parenchyma is so slight that tests such as the urea clearance do not reveal any damage to the excretory apparatus

Splanchnic section, by the release of vasoconstrictor influences, might decrease the blood pressure to the same degree as could be accomplished by rest in bed and sedation The effect of the operation would not be sufficient to permit the blood pressure to return to normal because the hypertension produced experimentally by the kidney pressor substances is unaffected by total sympathectomy, as Freeman and Page (1937) and others have shown In this patient, denervation of the adrenals would be expected to relieve headaches, to lessen cardiac oppression and to effect a general quieting of the patient's nervousness, sleeplessness, *etc* Such a stage is believed illustrated in Case Record 2

Case Record 2—C G, white, female, age 43 Father died of dropsy, one sister has hypertension Developed hypertension during her first, and only pregnancy at age of 28 Blood pressure as high as 205/140 before delivery On discharge from Maternity Hospital, blood pressure 128/68 Three years later, blood pressure 160/100 Complained at that time of nervousness Two years after this, N P N 29 mg per cent P S P 60 per cent in two hours In 1938, entered hospital with blood pressure averaging 238/140 Complaints were constant headaches, 13 years, hysterical crying spells, two years, dizziness with fainting, five years, palpitation, ten years, insomnia, ten years Eyegrounds showed moderate arteriolar sclerosis Moderate cardiac enlargement Laboratory tests showed urea clearance 84 per cent Urea N 12 mg per cent Highest specific gravity of urine attained 1.025 Bilateral splanchnic section, November, 1938 Blood pressure 17 months after operation, 230/130 Patient has been free of headaches and palpitation She is less nervous She tires more easily than before operation Sleeps without sedatives Considers operation has been definitely beneficial

Consider, thirdly, a stage of the disease in which the functional constriction of the renal vessels has led to actual occlusive disease of these vessels Retinal arteriolar sclerosis is definite Renal function tests show a 50 per cent diminu-

tion in urea clearance The blood pressure level is high with the diastolic pressure fixed at about 130 Mm Hg Symptoms associated with the hypertension are marked Depression of the blood pressure on rest in bed is insignificant Splanchnic section could not be expected to lower the blood pressure as the renal vessels are narrowed by pressor substances and occlusive disease to a point where any narrowing due to nervous influences is insignificant Adrenal denervation would effect symptomatic improvement because of its influence on the nervous system and the elimination of blood pressure crises

Case Record 3—White, male, age 40, single Known to have had high blood pressure for a year Recently, has had marked dyspnea on exertion, fatigues easily, unable to work Blood pressure 235/125 Heart definitely enlarged to left Eyegrounds show minimal arteriolar sclerosis ECG shows definite myocardial damage Urea clearance 50 per cent of normal Highest specific gravity in urine concentration test 1.012 Urine shows plus albumin Bilateral splanchnic section, March, 1938 Two years after operation, patient is working every day Urine shows trace of albumin Heart enlargement is less than before operation Dyspnea less than before operation No headaches Blood pressure averages 215/135

Consider, fourthly, a stage of the disease in which there is widespread occlusive disease of the renal vessels There is diffuse retinal arteriolar sclerosis with extensive hemorrhage The blood pressure is markedly elevated, with the diastolic fixed at 130 Mm Hg or over It is not modified by rest in bed and sedation Renal function tests show 25 per cent, or less, of the normal amounts of urea clearance Symptoms from the hypertension are very marked

Splanchnic section would not affect the blood pressure Symptomatic relief could still be afforded Progression of the disease would probably not be interfered with Case Record 4 is taken to illustrate this stage

Case Record 4—H. B., white, female, age 47 Married and has two grown children Father died of cardiorenal disease, mother of kidney trouble Hypertension for five years Complaints were headache, palpitation, cardiac asthma, dyspnea on exertion, nervousness Blood pressure 260/140 No depression of blood pressure with rest in bed and sedation Eyegrounds show moderate arteriolar sclerosis Urine specific gravity 1.005 Urea clearance 15 per cent NPN 50 mg per cent Moderate enlargement of heart Bilateral splanchnic section, February, 1938 One year later, patient free of headaches, palpitation less, fewer attacks of "cardiac" asthma, less nervous, living fairly normal life Blood pressure 230/130 Urea clearance 23 per cent One year and nine months after operation, patient free of headaches, slight edema of ankles which disappeared on low salt intake Both patient and family satisfied with results of operation Blood pressure 240/130 Urea clearance 12 per cent Twenty-three months after operation, developed a cerebral hemorrhage—death within three days

Surgery for Hypertension—An analysis of our records thus shows a close correlation between the expected and the actual result of splanchnic section for hypertension Splanchnic section can reduce blood pressure to normal where nervous influences are initiating the train of events which lead to a permanent stage of the disease process It is believed that the only clinical evidence justifying the assumption that nervous influences still dominate the picture is to be found in the demonstration that the elevated systolic and diastolic pres-

tures will return to normal on rest and sedation. Splanchnic section will not lower blood pressure appreciably once the renal ischemia is effected by mechanisms not under nervous control. Symptomatic relief from "nervous" symptoms will be afforded in over 70 per cent of the cases. This, for reasons given, is considered an effect of the adrenal denervation. It is secured regardless of the effect on blood pressure. Evidence has not yet been accumulated for sufficiently long periods on a large enough number of cases to warrant any statement as to the influence of splanchnic section on the progress of the disease.

In the author's opinion, the rôle for the surgeon in the problem of hypertension is to determine whether or not and in what types of cases renal-adrenal denervation performed at the very onset of the disease, before there is any fixed blood pressure elevation, will effect a permanent drop in blood pressure and restore renal circulation to normal. He will, thus, solve the question as to what part the nervous system plays in the initiation of the disease. He will doubtless also secure evidence as to the frequency with which causes other than nervous ones are responsible for the initiation of the hypertensive state. Only when such evidence is available will it be possible to select the cases suitable for splanchnic section.

SUMMARY AND CONCLUSIONS

Essential hypertension results when there is narrowing of peripheral arterioles with a maintained cardiac output. The vascular narrowing, presumably, is effected by a renal pressor substance released during a state of renal asphyxia.

It is believed that the initiation of the renal arteriolar narrowing necessary to bring about the renal asphyxia may be effected by nervous or humoral influences.

Regardless of the manner of its initiation, the process can become self-perpetuating. Neither nervous nor endocrine influences need, thereafter, play an essential rôle.

It is regarded as highly probable that hypertension occurs particularly in persons whose blood vessels are so constituted that they respond hyperdynamically to vasopressor influences. If such pressor influences are present in abnormal amounts, even normal renal blood vessels may constrict sufficiently to initiate renal ischemia.

Experimental and clinical evidence is cited to show that continued functional narrowing of blood vessels leads to occlusive narrowing. The degenerative changes characteristic of the occlusive disease are presumed to follow interference with the function of the vasa vasorum.

Splanchnic section may be expected to relieve renal ischemia initiated by vasoconstrictor influences if the renal ischemia has not become self-perpetuating.

Evidence that epinephrine lowers the threshold for excitatory influences on

the nervous system and increases the magnitude of the cortical response to identical peripheral stimuli is presented

The symptomatic relief afforded by splanchnic section, in cases where there is no drop in blood pressure, is considered due to adrenal denervation

Experimental evidence that a substance produced as a consequence of renal ischemia may increase, in certain animals, the tone of the smooth muscle of the iris and nictitating membrane is reported Under such circumstances the effect of exogenous epinephrine on these structures is also enhanced

Typical case records showing the effect of splanchnic section at various stages of hypertensive disease are presented

A rôle for the surgeon in the solution of the problem of essential hypertension is to determine the number and types of cases in which nervous influences set into activity the mechanism by which hypertension is initiated This can be done only if cases are treated in their initial stage

BIBLIOGRAPHY

- ¹ Allen, F P Jour Int Hygiene, 13, 164, 1931
- ² Barker, N W, and Walters, W Proc Staff Meet Mayo Clinic, 13, 118, 1938
- ³ Corcoran, A C, and Page, I H Am Jour Physiol, 126, 354, 1939
- ⁴ Craig, W M, and Adson, A W Surg Clin North Amer, 19, 969, 1939
- ⁵ Cushing, H Bull Johns Hopkins Hosp, 50, 137, 1932
- ⁶ Donison, C P Lancet, 1, 6, 1929
- ⁷ Freeman, N W, and Page, I H Am Heart Jour, 14, 405, 1937
- ⁸ Gannon, G D Jour Clin Invest, 15, 153, 1936
- ⁹ Goldblatt, H, Lynch, J, Hanzal, R F, and Summerville W W Jour Exper Med, 59, 347, 1934
- ¹⁰ Grimson, K S, Bouckaert, J J, and Heymans, C Proc Soc Exper Biol and Med, 42, 225, 1939
- ¹¹ Harrison, T R, Blalock, A, Mason, M F, and Williams, J R, Jr Arch Int Med, 34, 545, 1936
- ¹² Heinbecker, P Amer Jour Physiol, 117, 686, 1936
Idem Am Jour Physiol, 120, 401, 1937
Idem, and Bishop, G H ANNALS OF SURGERY, 107, 270, 1938
- ¹³ Hines, E A, and Brown, G E Ann Int Med, 7, 209, 1933
- ¹⁴ Jensen, Julius Am Heart Jour, 5, 763, 1930
- ¹⁵ Page, I H Science, 89, 273, 1939
- ¹⁶ Page, I H, and Hilmer, O M Jour Exper Med, 71, 29, 1940
- ¹⁷ Peet, Max Trans Amer Surg Assn, 57, 524, 1939
- ¹⁸ Pickering, G W, Kissin, M, and Rothschild, P Clin Sci, 2, 193, 1935
- ¹⁹ Raab, W Ztschr f klin Med, 118, 618, 1931
- ²⁰ Smith, Homer W Physiology of the Kidney Lawrence, Univ of Kansas Press, 1939
- ²¹ Tigerstedt, R, and Bergman, P G Skand Arch Physiol, 8, 223, 1898
- ²² Verney, E B, and Vogt, M Quart Jour Exper Physiol, 28, 253, 1938
- ²³ Weitz, W Hypertension Leipzig, 1926
- ²⁴ White, H L, and Heinbecker, P Proc Soc Exper Biol and Med, 43, 7, 1940
- ²⁵ Winternitz, M C, Thomas, R M, and LeCompte, P M The Biology of Arteriosclerosis Baltimore, C C Thomas, 1938

FACTORS INFLUENCING THE PROGNOSIS IN OSTEOGENIC SARCOMA^{*}

BRADLEY L. COLEY, M.D.

AND

JOHN L. POOL, M.D.

NEW YORK, N. Y.

FROM THE BONE TUMOR DEPARTMENT, MEMORIAL HOSPITAL, NEW YORK, N. Y.

ANYONE who has had an opportunity of following a considerable number of cases of osteogenic sarcoma over a period of years must admit that the results of treatment are not encouraging. The clinician is baffled by the fact that, while approximately four-fifths of all cases terminate fatally in less than five years, an explanation of why the other one-fifth survive is still lacking.

That a number of factors combine to influence the prognosis seems obvious. We feel that the resultant of all these factors determines, in a given case, whether the patient will succumb or survive.

With a view toward attempting to evaluate these factors, we have recently studied a group of 217 cases of osteogenic sarcoma observed at the Memorial Hospital. Included are 53 cases without microscopic confirmation, and, in addition, an indeterminate group of four cases (see Table IX). Excluding these 57 cases, we have a determinate group of 160 cases, all with microscopic confirmation. Of these, 121 are listed as failures, 117 having died of sarcoma, and four others with the disease still present being lost to follow-up. There remain 35 cases free of disease five years after treatment, which, based on the determinate group, gives a five-year survival rate of 22 per cent.

Among the factors we have considered are Age, sex, interval elapsing between onset of symptoms and amputation of limb, anatomic location of tumor, biopsy, histologic grading of tumor, and nature of treatment employed.

Age Incidence—The material has been divided into what seems to be significant age-groups, that is, each embracing a decade (Table I). While no age-group is immune, the peak incidence occurs in late adolescence. The most significant inferences concern patients in the first decade. Here, regardless of duration, symptoms or histologic pattern, the prognosis is exceedingly bad¹. In patients over 40 the prognosis is nearly as bad. There were 46 patients from 40 to 70 years of age. Of these, six or 13 per cent survived. Included were nine with Paget's disease on which osteogenic sarcoma was secondarily engrafted. The ages of the latter ranged from 43 to 63. Of these, but two survived, one an ilium case and the other a femur.

Sex Distribution—Of the 160 cases, 100 or 60 per cent were males.

^{*} Presented by title before the American Surgical Association, St. Louis, Mo., May 1, 2, 3, 1940.

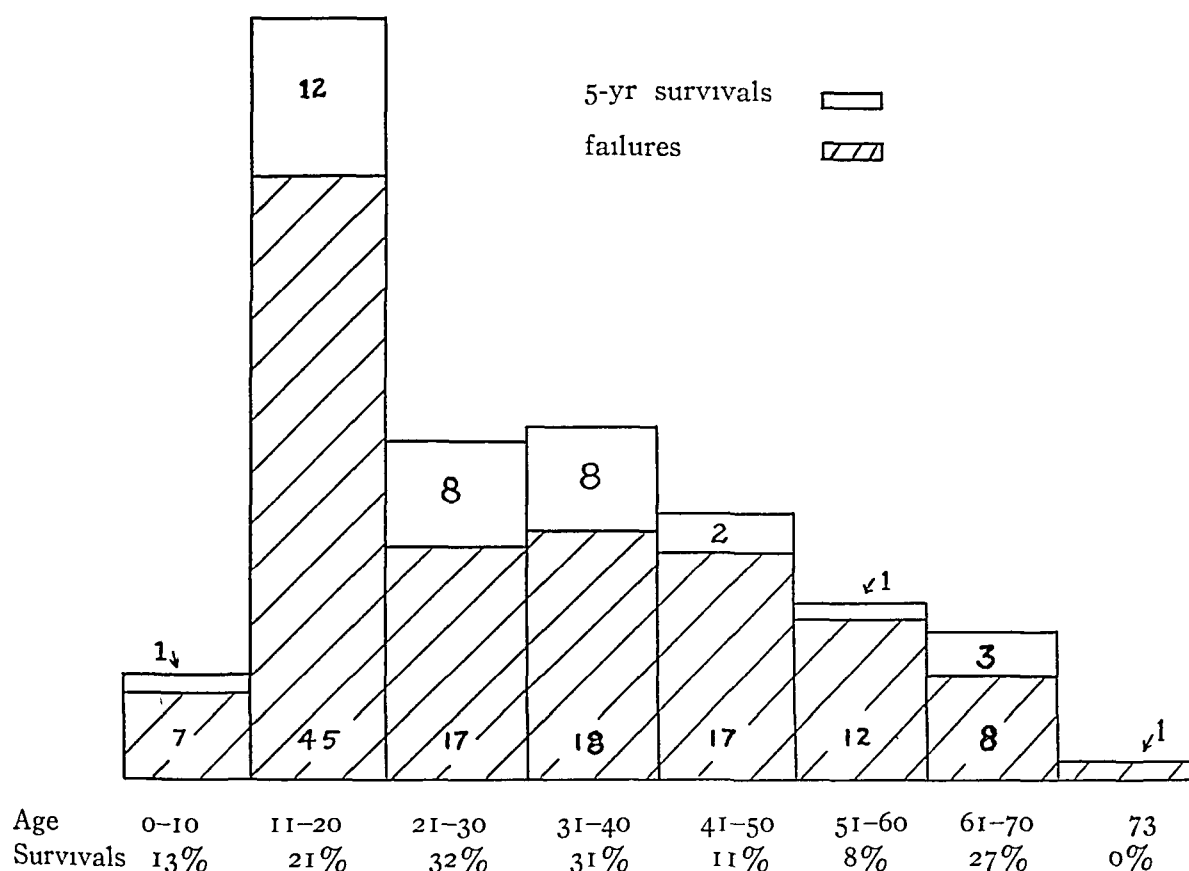
OSTEOGENIC SARCOMA

TABLE I

AGE INCIDENCE

Memorial Hospital Series, 1917-1935

160 Cases, Proven Histologically—35 Five-Year Survivals



However, the survival rate of the females was 28 per cent as compared with 18 per cent in the males. We are unable to account for this apparently better prognosis in the female (Table II)

TABLE II

SEX DISTRIBUTION

	Total	Dead of Disease	5-Year Survivals
Male	100	82	18
Female	60	43	17
Totals	160	125	35

Pathologic Fracture—This complication, which occurred in 15 cases, or approximately 10 per cent of the total number, might be expected to have a serious influence on the prognosis. In an earlier communication,² 21 per cent of 122 cases had this complication, and the duration of life averaged ten months less than in the cases without fracture. In this study, we found that in the fatal cases the duration of life was halved. One would expect, how-

ever, that cases with fracture would show a survival percentage much lower than the cases without fracture. Early pathologic fracture is seen most often in rapidly growing, histologically malignant tumors. The factor of fracture itself, by producing intratumoral hemorrhage and favoring the liberation of cell emboli in the manner in which fat emboli are discharged after uncomplicated fractures, would seem to be of importance. Yet, of the 15 cases, three survived, giving a rate of 20 per cent, which is only slightly lower than that for the series as a whole (22 per cent).

Interval Elapsing Between Onset of Symptoms and Amputation—A comparative study of the failures and successes shows that there was an interval of one year or more in 18 per cent of the patients that died, and in 22 per cent of those that survived. This variation is not significant. It does seem important to consider the causes of this procrastination. While in some the mildness of the symptoms was apparently responsible, in the majority it may be attributed to failure to make a correct diagnosis, resulting in a loss of time while improper treatment was being administered. Failure to make roentgenologic examination of a painful extremity is the commonest error, and sometimes an inadequate examination was responsible. The roentgenograms should include a considerable area proximal to the point of pain, and views in several planes and stereoscopically are advisable.

In the group that died, the 37 per cent who came for early treatment all had highly malignant tumors. A large majority of those in the first decade and in the first half of the second decade also had tumors of high malignancy. The patients who delayed for from three to 12 months include many who had relatively low-grade or peripherally situated tumors, yet these tumors because of the delay, had had time to metastasize. It is believed that earlier treatment would have cured some of these patients.

In the five-year survivals, the longest interval between onset and treatment occurred in the case of a female, age 29, with a low-grade chondrosarcoma expanding the anterior portion of the left fifth rib. She waited for seven years after first noticing the swelling in this rib before seeking medical advice. Another patient, who waited for five years, had a medullary chondrosarcoma involving the lower two-thirds of the left humerus—a slowly growing but definitely malignant tumor.

Anatomic Location of Tumor—Our study discloses that the femur, especially the lower third, is the most frequent site, with the upper ends of the tibia, the humerus, and the fibula, ranging in order. In the tubular bones, osteogenic sarcoma occurs most frequently in the metaphyseal region, tending to invade both the epiphysis and diaphysis secondarily. That it should occur most readily in the metaphyseal regions of greatest growth is not surprising.

The peripheral sites of origin apparently offer a better prognosis than do those more centrally located, thus, osteogenic sarcoma of the bones of the forearm and of the feet gives a better than 50 per cent prognosis. Also notable is the femur, no survivals occurred in cases primary in the middle or upper third, although some cases surviving five years with a primary site in

the lower third of the bone did have extension more than a third of the way up the shaft

The mortality for osteogenic sarcoma located in the flat bones and the

TABLE III

PRIMARY SITE IN 160, HISTOLOGICALLY
PROVEN, CASES OF OSTEOGENIC SARCOMA

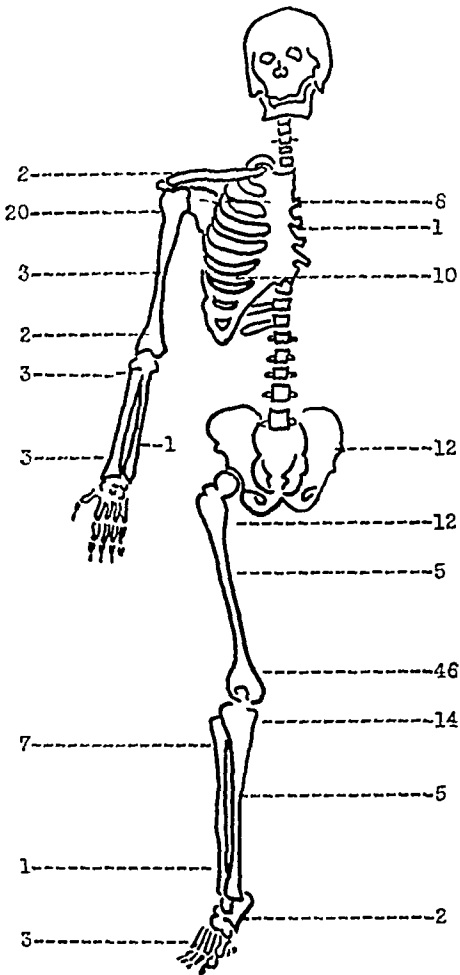
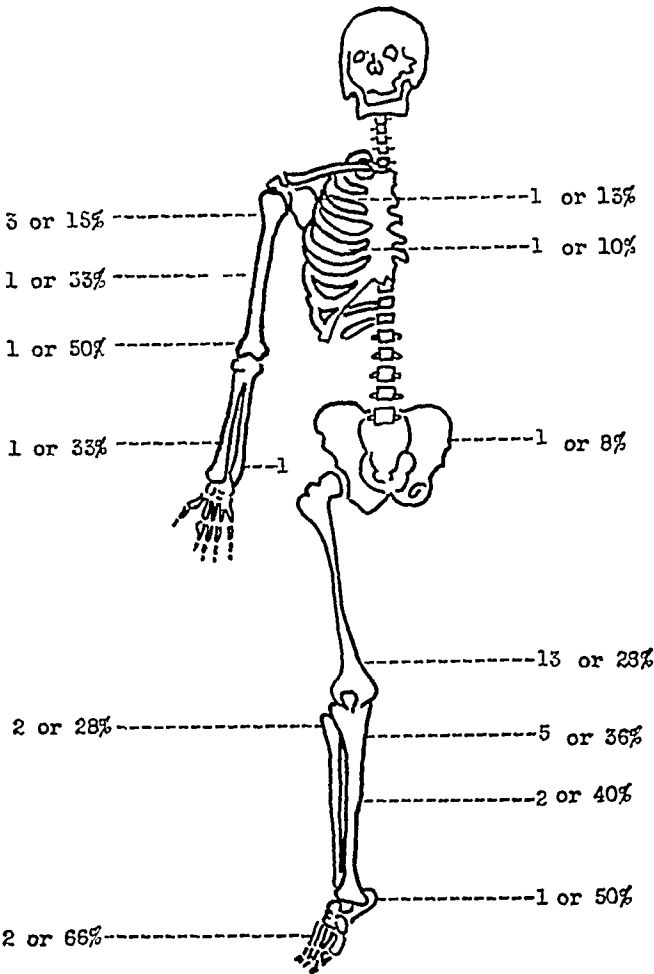


TABLE IV

PRIMARY SITE IN 35 PATIENTS WHO SURVIVED
FIVE YEARS FROM TIME OF TREATMENT



ribs is worse even than that for osteogenic sarcoma in the extremities, in this series one of each survives (Tables III and IV)

Biopsy—Aspiration biopsy, in our hands, has proven an excellent method for establishing the diagnosis, and has been successful in over three-fourths of the cases in which it has been attempted

The use of open surgical biopsy, despite the inherent theoretic dangers, has a definite place. In our series, 58 such biopsies were performed—42 in the unsuccessful and 16 in the successful groups. The inadvisability of resorting to radical surgery without a pathologic confirmation of the diagnosis is well known. In selected cases, properly performed biopsies were not followed by complications and even when amputation had to be performed in the course of the next week or two, there was no apparent increase in the mortality rate. Fungation and ulceration have followed improperly per-



FIG 1



FIG 2

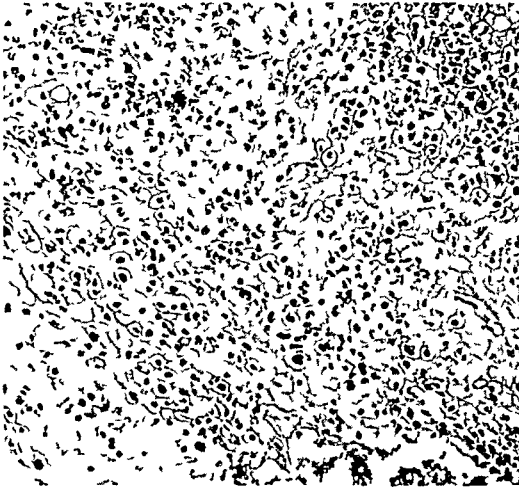


FIG 3

FIG 1—A low grade chondrosarcoma showing well defined demarcation between cartilage and fibrous capsules ($\times 45$)

FIG 2—A low grade periosteal fibrosarcoma showing relative uniformity of cell moderately well defined structure of fiber bundles and poor vascularity ($\times 45$)

FIG 3—An average chondrosarcoma in which cells are numerous. Nuclei tend to be large and variable in shape and staining. Intercellular substance is moderate in amount ($\times 45$)

FIG 4—A cellular spindle cell osteogenic sarcoma of medullary origin and average malignancy ($\times 45$)

FIG 5—A high grade osteogenic sarcoma showing cell pleomorphism telangiectasis and a mucoid stroma ($\times 120$)

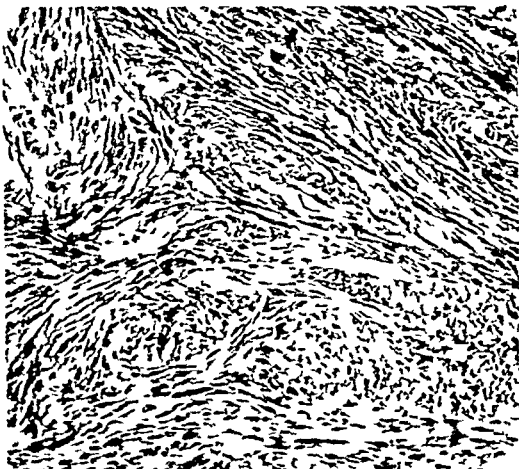


FIG 4

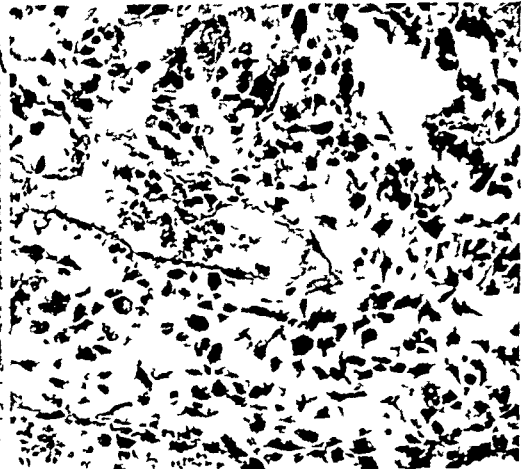


FIG 5

formed biopsies. Probably, the procedure should be, to reserve open biopsy for cases in which the aspiration method has failed. If an immediate amputation is decided upon, the biopsy should be performed, using a tourniquet so that the amputation can be carried out at once if the pathologist's report on the frozen section or smear is that of sarcoma.

These open biopsy wounds should invariably be closed without drainage and never packed. Failure to observe this precaution has resulted in fungation of the wound, secondary infection, and alteration of the growth rate, thus precluding adequate later treatment.

Pathology—The grade of malignancy encountered must be determined by an evaluation of a number of factors. The gross pathologic picture is important, for it shows the presence or absence of invasion into the epiphysis, whether the tumor is medullary, periosteal or both in its extent, and whether the adjacent soft parts are invaded. Extension of tumor tissue for a considerable distance up the narrow cavity, invasion of the femoral or axillary vein, extensive infiltration of overlying soft parts, tissue of a telangiectatic character, all are of extremely unfavorable significance, conversely, their absence is more favorable.

Microscopically, the grade of malignancy is demonstrable by a uniformity or pleomorphism of the cell type and we feel that in a given case, the most highly malignant area seen under the microscope should determine the grade. That such grading of the tumor is of importance in the outcome of the case is seen in Table V, which indicates a survival rate of 40 per cent for low-, 16 per cent for average-, and 15 per cent for high-grade tumors. The fact that the average- and the high-grade tumors have an almost identical survival rate might indicate that histologic criteria of the two groups are less distinct than are those of tumors of low-grade malignancy.

TABLE V
OSTEOGENIC SARCOMA
Pathology

(1) Patients dead of disease		125
a Tumor of low-grade malignancy	21 or 17%	
b Tumor of average-grade malignancy	82 or 65%	
c Tumor of high-grade malignancy	22 or 18%	
Total	125	
(2) Patients surviving five years		35
a Tumor of low-grade malignancy	15 or 43%	
b Tumor of average-grade malignancy	16 or 46%	
c Tumor of high-grade malignancy	4 or 11%	
Total	35	

In other words, of 36 cases with tumors of low-grade malignancy, 40 per cent survived five years, of 98 with tumors of average-grade malignancy, 16 per cent survived five years, and of 26 with highly malignant tumors, 15 per cent survived five years.

Methods of Treatment—Amputation Amputation has been, and still is, the most generally accepted method of treating operable osteogenic sarcoma. There are, however, exceptional cases in which less radical surgical measures may be indicated. That amputation should be performed at once and without recourse to radiation is debatable.

Of 92 cases subjected to amputation, there were three operative deaths, in each instance the operation was carried out at another hospital.

Of the remaining 89 cases, 60 died of the disease and 29 lived for five years or more, a survival rate of 32 per cent.

Analyzing this group still further we find the following: Of 17 cases treated by amputation alone, five, or 29 per cent, survived five years, of 21 cases treated by amputation after preliminary surgery, seven, or 33 per cent, survived five years, of 41 cases treated by amputation after radiation, 14, or 34 per cent, survived five years.

Table VI shows the deaths and survivals in those cases amputated during the first six months, in the second six months, and one year or more after the onset of symptoms.

TABLE VI

ANALYSIS OF RESULTS IN 89 CASES OF OSTEOGENIC SARCOMA SUBJECTED TO AMPUTATION

	Total	Dead of Dis- ease	5-Year Survival	Per Cent	1 to 6 Months*		7 to 12 Months		13 Months Plus	
					Dead of Dis- ease	5 Year Survival	Dead of Dis- ease	5-Year Survival	Dead of Dis- ease	5-Year Survival
Total subjected to amputation	89	60	29	32	35	7	15	9	10	13
Amputation only	17	12	5	29	4	3	6	1	2	1
Amputation after preliminary conservative surgery	21	14	7	33	10	3	2	2	2	2
Amputation after radiation	41	27	14	34	18	1	5	5	4	8
Amputation after radiation and other surgery	10	7	3	30	3	0	2	1	2	2

* Interval of time in each case refers to months elapsing between first appearance of tumor and date of amputation.

In general, this table tends to support Ferguson's⁷ assertion, based on a somewhat similar survey of cases on file with the Bone Sarcoma Registry, that the cases in which amputation was performed *after* a lapse of six months from the appearance of the first symptom showed a higher percentage of five-year survivals than did those in which amputation was performed during the first six months. In our opinion, however, it has by no means been established that delayed amputation was responsible for the better results. The question naturally arises: Why were some amputations performed at once and why were some delayed? We offer the following answer: Those cases amputated early had much more rapidly growing, symptom-producing tumors, and represented tumors of a higher degree of malignancy as shown by the histologic grading. For example, Forty-two cases were amputated within six

months of onset of symptoms. Only three, or 7 per cent, were low-grade tumors, and 21 per cent were highly malignant. The survival rate was 16 per cent for this group. Cases amputated between six and 12 months after onset showed eight out of 24, or 33 per cent, low-grade tumors, the group as a whole had a survival rate of 39 per cent, and a 50 per cent survival in the low-grade tumors. Cases in which amputation was delayed for more than a year (23) included eight, or 35 per cent, low-grade osteogenic sarcomata. Here the survival rate was 56 per cent for the whole group, and 62 per cent for the low-grade tumors. *The proportion of lower degrees of malignancy thus, bears some ratio to the survival rate.*

We believe that delay, of itself, is undesirable, and, if generally practiced, will result in fewer survivals. If, for any reason, a delay is enforced upon the surgeon, then heavy radiation with roentgenotherapy should be administered in the interval. Less harmful effects of procrastination are apt to follow this practice. We have not observed, except in cases heavily radiated, any rhythmic periods of activity and quiescence, as described by Ferguson. Nor do we believe that excision is useful in "creating a proper time to amputate." Excision should be reserved for exceptional cases both as to anatomic considerations and low-grade malignancy.

If, when the patient is first seen, tumor cells are assumed to be in the circulating blood, we doubt that radiation, resection or amputation can exert any inhibitory action upon them. This highly desirable effect, we believe, must await a more efficient systemic agent than has as yet been discovered. The effect of bacterial products on certain malignant tumors in animals seems a possible lead in this direction.

Level of Amputation—The dictum that amputation should be carried out at least at the next higher joint and never through the bone involved is, in our opinion, without support. While admitting that, in most instances, it is desirable to avoid transecting the affected bone, we do not feel that a hip-joint disarticulation should be recommended for every osteogenic sarcoma of the lower end of the femur. The results would seem to show that hip-joint disarticulation is not more effective than subtrochanteric amputation where judgment is used in the selection of cases for the less radical procedure. We believe it significant that of the 29 five-year survivals treated by amputation, 15, or more than 50 per cent, were amputated through the bone involved, four were disarticulated through the proximal joint, and ten were amputated through the proximal bone (including interscapulothoracic amputations). Furthermore, there were 43 femur cases treated by amputation, of which four had hip-joint disarticulation, with no survivals. Of the remaining 39 in which high thigh amputation was performed, there were 12 survivals (Table VII).

Resection—Resection was attempted in 17 cases. There were only two five-year survivals, *i e.*, a rib and a tibia. Resection always carries the risk of a recurrence which calls for further operation and, perhaps, late amputation.

TABLE VII
SITE OF AMPUTATION

	No of Cases	Failures	5-Year Survivals
Submitted to amputation	92		
Suitable for end-result study	89		
Amputated through bone involved	42	27 to 65%	15 or 35%
Amputated through <i>joint</i> proximal to bone involved	19	15 or 78%	4 or 21%
Amputated through <i>bone</i> proximal to bone involved*	28	18 or 65%	10 or 36%
Totals	89	60 or 66%	29 or 33%

* Includes interscapulothoracic disarticulation

Radiation—Radiation alone was employed in 35 cases, with 32 deaths and three five-year survivals. In the latter, the tumor was located in the tibia, humerus and ilium. In two cases, the tumor was superficially located without much soft-part tissue between it and the source of radiation. All received heavy radiation. In one case, interstitial radiation by means of removable radon needles was administered in addition to external radiation with the radium element pack. It should be especially noted that in each instance the tumor was of a low-grade, slowly growing type.

Radiation as a preoperative measure will often alleviate pain and sometimes cause a diminution in the size of the tumor, thus rendering it operable. Radiation may hold the disease in check while the patient and his family are being convinced of the necessity for amputation.

One must conclude that preoperative radiation is worthy of a continued trial from the fact that of 41 cases in this series treated by amputation after radiation, 34 per cent lived for five years—a slightly higher percentage than was obtained in the groups treated by amputation alone or amputation following preliminary surgery.

In the following three cases the patients survived five years following radiation therapy alone.

Case 1—B S R No 1453 G R, female, age 36. In February, 1929, a swelling was noted on the anterior aspect of the proximal third of the left arm. This slowly increased in size, and an incisional biopsy was performed 11 months later. Four months thereafter, the patient was examined by Doctor Ewing, at the Memorial Hospital, who made a diagnosis of periosteal fibrosarcoma on the biopsied tissue. Roentgenologic examination revealed no bone destruction. During the course of 20 days, the patient received a tissue dose of 4,700 r to the tumor (one-third by external radiation with the 4 Gm element pack, and two-thirds with platinum filtered removal needles). At the present time, nearly ten years later, the arm function is normal, although there is marked fibrosis at the site of the tumor.

Case 2—H F, male, age 21, in June, 1931, struck his right shin a sharp blow against the rim of a barrel. A hematoma developed which did not absorb. Roentgenologic examination revealed an expansile, central, cystic area of destruction in the lower third of the tibia. Doctor Ewing examined a biopsy section and reported it to be a low-grade fibrosarcoma of medullary origin. A tissue dose of 900 r (200 K V) was administered to the upper and lower half of tumor, which had shown no further increase in size. Similar smaller cystic defects have been noted in other tubular bones.

Case 3—B S R No 1517 S G, male, age 59, first noticed pain in the region of the right hip in February, 1930. This was followed six months later by weakness of the right leg on standing, and a swelling in the groin one year later. Nearly three years after the onset of disability, a physician was consulted who referred the patient to the Memorial Hospital. Roentgenologic examination revealed a huge, destructive, osteolytic, expansile process of the right ilium. There was also evidence of Paget's disease in the femora, tibiae and humeri. A punch-biopsy section from the ilium was examined and pronounced an osteogenic sarcoma of spindle and giant cell type. Between January 31 and May 1, 1931, a tissue dose of 3,200 r (200 K V) was administered. There was progressive flattening of the acetabulum but 18 months later the tumor showed complete recalcification which remained unchanged until the patient's death in January, 1940. One year previously, the radiated skin in the groin had become ulcerated, but the patient refused further hospitalization and died as an indirect result of this ulceration but without evidence of active sarcoma (Table VIII).

Toxin Treatment—(The mixed toxins of erysipelas and *Bacillus prodigiosus*, or Coley's toxins). The toxins were administered in 91 cases in this series, of which 20 survived. The part they played in the five-year survivals is very difficult to evaluate. They seem definitely indicated during the post-operative period in young individuals and, in general, in combination with amputation and possibly preoperative radiation in highly malignant tumors. The recent experimental studies of Schwartzman and his associates,⁶ Anderson, Fogg, Jacoby and others, on the effect of bacterial products on malignant tumors, are confirmation of the fact brought out many years ago by Fehleisen,⁸ W B Coley,⁹ Lassar¹⁰ and Spronck¹¹ that bacterial products sometimes exert a profound effect upon malignant tumors.

TABLE VIII

METHODS OF TREATMENT OF 144 CASES OF OSTEOGENIC SARCOMA*

	Total	Dead of Dis- ease	5-Year Sur- vival	1 to 6 Months		6 to 12 Months		13 Months Plus	
				Dead of Dis- ease	5-Year Sur- vival	Dead of Dis- ease	5-Year Sur- vival	Dead of Dis- ease	5-Year Sur- vival
Amputation only	17	12	5	4	3	6	1	2	1
Amputation following biopsy	15	12	3	9	2	2	1	1	
Amputation following radiation	41	27	14	18	1	5	5	4	8
Amputation following resection	4	1	3	1			1		2
Amputation following curet- tage	2	1	1		1			1	
Amputation following radiation and resection	6	4	2	2		1		1	2
Amputation following curet- tage and radiation	4	3	1	1		1	1	1	
Resection only	17	15	2	6		4		5	2
Radiation only	35	32	3	22	1	7		3	2
Curettage and radiation	3	2	1	2				1	
Totals	144	109	35	65	8	26	9	19	17

* Of the entire group of 160 cases 16 were unsuitable for this analysis. 15 Three died following operation elsewhere, nine had only palliative treatment following metastases and four were too far advanced for treatment.

Further experimental work along the lines of treatment by bacterial products is, undoubtedly, necessary. While for osteogenic sarcoma we are not prepared to claim for the toxins any well-established therapeutic effect in the prevention of metastasis, we still feel that their use following amputation is worth while, particularly is this true of the highly malignant anaplastic types which have an exceedingly unfavorable prognosis by amputation alone.

An evaluation of the effect of the various methods of treatment and of the histologic character of the tumor present is best approached by a consideration of the problems raised in the individual case. In the following ten cases, we have tried to weigh carefully all the favorable and unfavorable features in an attempt to explain why the patient did or did not survive.

Case 4—G. M., male, age 16, noticed a swelling in the midshin ten days after a direct trauma. This diminished but never entirely disappeared, and because of increasing local pain, the patient appeared at the Memorial Hospital nine months later. The pain was relieved by a moderate dose of 200 K V roentgen ray, amputation was performed four months after admission.

In this patient's favor are the following: (1) That he is in later adolescence, (2) that a relatively peripheral bone is involved, and (3) that the tumor responded, at least somewhat, to radiation, as indicated by relief of pain. On the other hand, there was a 13 months' delay between the onset and the amputation. While the specimen shows a tumor partially cartilaginous, it invades the epiphysis and the soft tissue. Microscopically, there are cartilaginous areas showing radiation effect, and also areas of highly malignant sarcoma. The patient has had no recurrence in ten years.

Case 5—M. B., female, age 15, had pain and swelling of the right knee over a period of two months. Roentgenologic examination showed an osteogenic sarcoma, partially sclerosing. Following two negative aspiration biopsies, a formal biopsy and immediate amputation were performed, after which a course of Coley's toxins was given. The patient has remained well for six years.

Although microscopic studies showed a highly malignant spindle and giant cell tumor, osteolytic in many areas, and despite the patient's age, prompt and decisive treatment resulted in a survival beyond the five-year period.

Case 6—G. K., male, age 31, noticed pain in the right knee for one and a half months before consulting his local doctor. The latter treated him with ointments, massage, and ultraviolet light for three months before sending him to the clinic. An immediate high thigh amputation was performed without a preliminary biopsy, following which a postoperative course of toxin treatment was instituted. Pulmonary metastasis appeared eight months later. Pathologically, this tumor of the lower femur was a low-grade chondrosarcoma. Its location, and the age of the patient were favorable factors but the early faulty treatment probably aided materially in disseminating the disease.

Case 7—J. H., female, age nine, was admitted two months after onset of pain in the midthird of the right arm. The lesion, as seen in the roentgenograms, was confirmed by aspiration biopsy. Despite a shoulder-joint disarticulation and strenuous course of Coley's toxins, metastases appeared, first in the left tibia, then in the femur, and finally in the skull and lungs. The tumor was a highly malignant chondrosarcoma, probably of periosteal origin. Here, despite the relatively favorable site and the prompt and strenuous therapy, the relative youth of the patient and the malignancy of the tumor determined the fatal outcome.

Case 8—R. B., female, age 16, complained of pain and rapid enlargement of the right upper arm over a period of two months. Moderate radiation and a course of toxins were administered for two months without visible effect on the tumor. A complete fracture occurred through the tumor and a disarticulation of the humerus was performed.

Pulmonary metastases appeared three months later. Pathologically, this tumor was medullary, subperiosteal, and had invaded the adjacent soft parts quite extensively—a factor which, with delay in amputation and the presence of a pathologic fracture, strongly influenced the outcome.

Case 9—J L, male, age 23, noticed pain and swelling one day after a light blow just below the knee. The patient came to the Memorial Hospital for treatment within the next four or six weeks. No biopsy was taken, but heavy dosage of gamma radiation was carried out for three months, followed by a mid thigh amputation and a course of toxins. Pulmonary metastases appeared one month later. The gross specimen showed a tumor filling the marrow cavity, invading the epiphysis, and even elevating the joint cartilage, there was also marked invasion of the adjacent soft parts. Microscopically, the tumor showed much calcification, and many large spindle and giant cells indicative of a high-grade of malignancy. Despite the favorable site and the prompt medical consultation, the disease had already spread elsewhere by the time that the leg was removed. Perhaps the delay incident to the preoperative radiation lost for this patient his chance of a cure.

Case 10—J S, male, age 12, had had a tonsillectomy performed because of pains about the left knee. Four months later, a roentgenogram was taken and the patient was kept under observation for another two months. At the end of this time, a swelling appeared. An aspiration biopsy yielded a diagnosis of osteogenic sarcoma, and the patient was referred to the Memorial Hospital for treatment (eight months after onset). A ten-day course of high voltage roentgenotherapy was followed immediately by a subtrochanteric amputation and a course of toxins. Examination of the gross specimen showed a sclerosing tumor, cystic and hemorrhagic where it had elevated and invaded the periosteum, and calcified where it had extended along the marrow cavity, which was involved for a distance of 18 cm.

TABLE IX

END-RESULTS IN OSTEOGENIC SARCOMA

Memorial Hospital Series, 1917-1934 Inclusive

	No. of Cases	
1 Clinical diagnosis (exclusive of maxilla and mandible)	217	
2 Without histologic verification of diagnosis	53	
3. With histologic verification (summarized for this study)	164	
a Indeterminate Group		
(1) Dead of other causes in less than 5 years, without recurrence	3	
(2) Lost to follow-up, without recurrence	1	4
	<hr/> 160	
b Determinate Group		
(1) Failures		
(a) Dead of sarcoma	121	
(b) Lost to follow-up, with disease	4	125
(2) Successes Free of disease 5 years or more after treatment	<hr/> 35	
4 Five-year survival-rate (determinate group)	22%	

In this case, many factors are against survival, especially the eight months of expectant treatment in the presence of a rapidly growing, highly malignant osteogenic sarcoma, the youth of the patient, and the site of the tumor, i.e., the middle third of the femur. Metastases became apparent one month following the amputation.

Case 11—This case represents an osteogenic sarcoma developing in Paget's disease. A male, age 63, complained of pain and stiffness about the left knee over a period of nine months. A huge tumor had developed. No treatment could be instituted, and at autopsy three months later, other osteogenic sarcomata, either metastatic or other primaries, were found in the right humerus and the right ilium.

TABLE X
SUMMARY OF FIVE-YEAR SURVIVALS OF OSTEOGENIC SARCOMA
Memorial Hospital Series, 1917-1934 Inclusive

No	Year	Nm	B S R	Sex	Age	Bone	Inter- val* (Mos)	Path Group	Surgery	Radi- ation	Tovins	Survival
												Yrs Mos
1	1918	B M	168	F	33	Femur	72	II	Amputation	x	x	13 8
2	1918	K F	373	F	29	Rib	48	I	Resection	x	x	17 10
3	1919	H S	172	M	19	Femur	11	I	Amputation	x	x	10 10
4	1920	L O	357	F	31	Humerus	12	II	Amputation	x	x	11 11
5	1921	I R	156	M	12	Humerus	17	II	Disarticulation	x	x	11 9
6	1921	J C	177	M	15	Tibia	4	I	Amputation	x	x	17 9
7	1921	J D	765	F	21	Femur	20	II	Amputation	x	x	10 5
8	1923	R M	833	F	8	Tibia	24	I	2 resections and amp	x	x	14 14
9	1925	C C	1352	F	34	Humerus	7	I	Disarticulation	x	x	14 9
10	1925	H N	921	M	16	Fibula	1	III	2 resections and amp	x	x	9 3† (Paget)
11	1926	I T	1437	F	63	Femur	16	I	Amputation	x	x	5 7
12	1928	T P	1117	F	37	Femur	13	II	Amputation	x	x	10 8
13	1928	J M	1773	M	38	Tibia	48	II	Resection and radon needles	x	x	9 7
14	1929	J S	1773	M	47	Tibia	19	I	Resection and amp	x	x	9 7
15	1929	G M	1444	M	16	Tibia	13	II	Amputation	x	x	5 5
16	1929	G R	1453	F	36	Humerus	11	I	Amputation	x	radon needles	9 4
17	1929	W H	1042	M	19	Femur	2	II	Resection and amp	x	x	10 5
18	1929	T S	1493	F	34	Metatarsal	8	II	Amputation	x	x	7 10
19	1929	T S	1493	F	19	Tibia	47	II	Amputation	x	x	5 7
20	1930	D W	1911	F	17	Femur	18	II	Amputation	x	x	9 5
21	1930	S K	1911	M	62	Femur	7	III	Amputation	x	x	2† (Paget)
22	1930	S G	1517	M	59	Ulna	36	II	Amputation	x	x	9 7†
23	1930	A S	1306	F	24	Ulna	8	III	Amputation	x	x	9 9
24	1930	J S	1306	M	65	Metatarsal	9	I	Amputation	x	x	8 7
25	1931	H F	1861	M	21	Tibia	3	I	Amputation	x	x	9 9
26	1932	B S	1861	M	43	Femur	31	III	Amputation	x	x	5 7
27	1932	D B	1441	F	15	Os calcis	4	I	Amputation	x	x	7 3
28	1932	S H	1441	M	17	Ulna	3	I	Amputation	x	x	7 7
29	1933	S G	1769	M	35	Scapula	35	I	Resection	x	x	5 5
30	1933	L B	1769	M	29	Fibula	20	I	2 resections and amp Partial pneumonectomy for metas 6 yrs later	x	x	4 5
31	1933	C T	1774	F	34	Humerus	3	II	Curettage and disarticulation	x	x	6 9
32	1934	M B	1767	F	15	Femur	2	II	Amputation	x	x	5 5
33	1934	A L	2065	M	21	Femur	5	I	Local exc and amp	x	x	5 5
34	1931	D G	1838	M	16	Femur	5	I	Amputation	x	x	5 5
35	1934	L B	2069	F	6	Femur	6	II	Curettage and amp	x	x	5 5

* Interval elapsing between appearance of tumor and treatment expressed in months
† Patients dead of other causes after five years without disease

In the following five cases the patients lived for five years or more and then succumbed to the disease

Case 12—B S R No 100 E P, female, age 23, first noticed a slowly growing tumor in the lower third of the right femur in December 1915. This was curetted 13 months later, and about 1,000 r by contact radium was administered. Six months later a mid thigh amputation was performed. The specimen proved to be a Grade I periosteal fibrosarcoma. No evidence of a recurrence of the disease was noted until 12 years later when metastases to the rib and pleura appeared, and the patient died within six months.

Case 13—A H, female, age 45, complained of persistent pain and swelling following a sharp blow received from a box falling on the dorsum of the left foot in 1922. An incisional biopsy was made three months later. The wound did not heal, and an amputation through the lower leg was performed one month thereafter. Pathologic examination showed an expansile tumor replacing the proximal four-fifths of the first metatarsal, made up of average malignant cells. Five years and four months later, metastasis appeared in the venous thrombi of the groin. A fungating mass was excised four months later, but the patient died at the end of two weeks from secondary hemorrhage.

Case 14—C G, male, age 59, noticed a slowly growing tumor in the upper aspect of the right thigh in 1925, or four years after a fracture of the right hip. When he presented himself at the Memorial Hospital, five years later, the tumor measured at least 13 cm in diameter. Aspiration biopsy revealed atypical cartilage cells, suggestive of a low-grade chondrosarcoma. No evidence of Paget's disease was noted. About 500 tissue dose (175 K V) was delivered to the tumor, and smaller doses repeated four and seven months later. The tumor remained unchanged in size, but three years later local pain developed and the patient died in another hospital from inanition and bronchopneumonia, six years after radiation.

Case 15—B S R No 1497 J S, female, age 14, developed a painful swelling in the lower third of the right femur which, in 1932, or two months after onset, was partially excised. A mid thigh amputation was performed one month later. Microscopic and roentgenologic examination showed the tumor to be composed of spindle cells of average malignancy, with little bone formation. Pulmonary metastases appeared five and three-quarters years later, but death did not follow for another year.

Case 16—L C, female, age 27, had pleuritic pains and febrile episodes in 1932, which were followed two years later by the appearance of a mass in the left axilla, and loss of 30 pounds in weight. Roentgenologic examination revealed a large tumor involving the third rib and obscuring the left upper lobe of the lung. This, on aspiration biopsy, proved to be an osteogenic sarcoma. Heavy radiation (700 K V) apparently imposed growth restraint. Two years later, an exophthalmic goiter was subtotally removed. Five and one-half years after therapy, involvement of the adjacent ribs became apparent and the patient died from extension of the disease within the chest.

SUMMARY AND CONCLUSIONS

A series of 160 histologically proven cases of osteogenic sarcoma treated between 1917 and 1933, at the Memorial Hospital, New York, has been studied from the standpoint of prognosis. In our opinion, the following factors have seemed to influence the outcome:

(1) *Age*—The prospect of five-year survival is most favorable in patients whose ages range from 20 to 40 years, and least favorable in those who are in the first decade or have passed through the fourth decade of life. Osteogenic sarcoma on a Paget's disease basis gives an extremely bad prognosis, these cases are usually found in the fifth, sixth and seventh decades.

(2) *Sex*—In our series the survival rate for females is 28 per cent

whereas that for males is 18 per cent—for which difference we are unable to account

(3) *Location*—In bones of an extremity, the more peripheral the lesion, the more favorable the outlook. There were no five-year survivals where the middle or upper femur was the site of disease.

(4) *Pathology*—A histologic grading of a tumor is of much value in estimating the outcome. Those of low-grade malignancy showed 40 per cent five-year survivals, those of intermediate, 16 per cent, and those of high-grade, 15 per cent.

(5) *Site of Amputation*—This was of interest to us because 35 per cent of the cases in which amputation was performed through the bone primarily involved, survived five years, whereas only 21 per cent survived amputation by disarticulation of the joint above, and 36 per cent survived amputation through the bone above. Although some authors maintain that one should never amputate through the bone primarily involved, our figures would indicate that for at least low femur tumors, indiscriminate hip-disarticulation was scarcely justified.

(6) Amputation alone or with preoperative conservative surgery (in exceptional cases), or with preoperative radiation, apparently remains the method of choice. It gave a 32 per cent survival (Table VI).

(7) Radiation alone was used in 35 cases, with three survivals, or 9 per cent. It seems unjustifiable to rely on this method alone unless the condition is inoperable or unless operation is refused.

(8) The five-year survival rate based on the *determinate* group (35 cases) was 22 per cent.

We wish to express our very great appreciation of the assistance rendered in this study by Dr. Fred W. Stewart, Pathologist of the Memorial Hospital.

REFERENCES

- ¹ Coley, B. L., and Peterson, R. L. Primary Bone Tumors in Children. *Am Jour Surg*, **ns**, 39, No. 2, 334-341, February, 1939.
- Idem*. *Jour Pediat*, **15**, No. 3, 327, September, 1939.
- ² Coley, B. L. Pathological Fractures in Primary Bone Tumors of the Extremities. *Am Jour Surg*, **9**, No. 2, 251, August, 1930.
- ³ Ewing, J. A Review of the Classification of Bone Tumors. *Surg, Gynec and Obstet*, **68**, 971-976, May, 1939.
- ⁴ Meyerding, H. W. Results of Treatment of Osteogenic Sarcoma. *Jour Bone and Joint Surg*, **20**, 933, October 1938.
- ⁵ Ferguson, A. B. Treatment of Osteogenic Sarcoma. *Jour Bone and Joint Surg*, **22**, No. 1, 92-96, January, 1940.
- ⁶ Schwartzman, G., and Morrell, S. A. *Jour Exper Med*, 671, 1938.
- ⁷ Walker, E. K., and Handman, M. S. *Jour Immunol*, **37**, 507, December, 1939.
- ⁸ Fehleisen. *Das Erysipel*, Berlin, 1888.
- ⁹ Coley, W. B. The Treatment of Malignant Inoperable Tumors with the Mixed Toxins of Erysipelas and B. Prodigiosus. *Trans Thrd Intern Cancer Conf*, Brussels, 1913.
- Idem*. *ANNALS OF SURGERY*, **14**, 199, 1891.
- Idem*. *Glasgow Med Jour*, **26**, 49, 128, August and September, 1936.
- ¹⁰ Lassar, O. *Deutsch med Wchnschr*, No. 29, 1891.
- ¹¹ Spronck, C. H. H. Tumeurs malignes et maladies infectieuses, *Ann de l'Institut Pasteur*, **883**, 1892.

MEMOIR

WILLIAM DAVID HAGGARD

1872-1940

IN THE DEATH of William David Haggard the surgical profession has lost a shining light, the American Surgical Association mourns a distinguished Fellow and his colleagues are deprived of a genial companion. If what is called "personality" counts for much in this world—and we must believe it does—the subject of this Memoir scores a high mark in the estimation of all those who knew him. It is difficult for one so intimate with him as the writer to put down in mere words a full, just and impartial tribute to this friend and associate over a period of 39 years. On the one hand, there is the temptation to paint the picture in too glowing colors, a natural tendency in a devoted compeer, on the other hand, a certain restraint impels the withholding of those expressions of the inner feelings, still saddened by a grievous loss.

William David Haggard was born in Nashville, Tennessee, September 28, 1872. In order to appreciate his qualities and to evaluate his career it is well to indicate his origin and his associations. His father, Dr. William David Haggard, Sr., a Kentuckian by birth, received his degree from the Jefferson Medical College of Philadelphia in 1851, practiced medicine for 24 years in Gallatin, Tennessee, and removed to Nashville in 1875. At once, he showed interest in medical education, becoming an assistant to the chair of gynecology in the Medical Department of the University of Nashville and Vanderbilt University, and was among the first in the South to accentuate the value of clinical teaching. In 1884, he was chosen as professor of gynecology and diseases of children in the University of Tennessee Medical Department, which had been established some years earlier by Paul F. Eve and W. K. Bowling.

The elder Haggard was a leader of his profession. As a teacher, for nearly a quarter of a century, he made a wholesome and ineffable impression upon the ambitions and practices of hundreds of young medical men throughout the South and West. He continued to fill his chair until his death. Higher standards of medical education found in him an early champion. The Southern Medical College Association selected him as its first president, and rapidly followed the example of the more wealthy colleges of the East in requiring a three- and then a four-years' graded course. He has the distinction of being the first president of the Southern Surgical and Gynecological Association, organized in 1887, and now known as the Southern Surgical Association.

The son followed in the footsteps of his father. He was graduated with first honors from the Medical School of the University of Tennessee in 1893.

Having served a term in the Woman's Hospital of New York, he returned to Nashville, became assistant to his father who conducted a private hospital, and, in 1901, following the death of his father, was advanced from associate



WILLIAM DAVID HAGGARD, M D

to the professorship of gynecology and abdominal surgery at his alma mater. In this position he continued until 1912, when the school was removed to Memphis. He was then elected professor of surgery and clinical surgery in the Vanderbilt University School of Medicine, which post he held at the time of his death, January 28, 1940.

To recount the various honors received, positions held, and offices per-

formed by Doctor Haggard is but to assert that in every organization, institution and establishment with which he was connected he went to the top. His capacity for leadership, for executive ability, for doing his own work well and inducing others to work with him was universally acknowledged. In professional circles he was the head of most of the associations to which he belonged—city, county, state, interstate, regional and national. Following is the list of organized medical societies over which, at one time or another, he presided: Nashville Academy of Medicine, Middle Tennessee Medical Association, Tennessee State Medical Association, Southeastern Surgical Congress, Southern Surgical Association, Inter-state Postgraduate Assembly, American College of Surgeons, American Medical Association. He held lesser offices in several of these organizations and was a member of many others. Of these may be mentioned the Society of Clinical Surgery, Pan American Medical Congress, International Society of Surgery. His Fellowship in the American Surgical Association began in 1916, continuing unabated, and with regular attendance, until his death, a period of nearly 24 years. In 1938 he was made a Senior Fellow.

In 1898, Doctor Haggard was married to Miss Mary Laura Champe, of Nashville, who died in 1920. Six years later he married Miss Lucille Holman, also of Nashville, who survived but six years. His children are three—a daughter, Mrs. Burgess Askew, Jr., and two sons, William David III, age 13 and John Holman, 11.

Doctor Haggard was a prolific writer and speaker. His best known collections are "The Romance of Medicine and Other Addresses" and "Surgery—Queen of the Arts, and Other Papers," both headed by the presidential addresses delivered before the two largest professional organizations in America. In addition, he was the author of numerous papers, dealing chiefly with goiter, surgery of the stomach and colon, and appendicitis.

His military record, familiar to his colleagues in World War No. 1, included Chairmanship of the Medical Section, Council of National Defense for Tennessee and medical aide to the governor, member of the Advisory Board, with rank of major. In the Surgeon General's office, Washington. Consulting surgeon, with rank of lieutenant colonel, M C U S Army, A E F, and surgeon, Evacuation Hospital No. 1, Toule, France, 1918-1919.

In his community relations Doctor Haggard was also a leader. He was president of his civic and social clubs, received the cup as the most eminent citizen, engaged in many enterprises for the improvement of his native city, won prizes at horse shows, served as an official in his church and was awarded the degree of D C L by the University of the South (Sewanee). On two occasions, when Doctor Haggard had received the highest acclaim of his profession he was greeted at home by his colleagues and fellow citizens who honored him by public demonstrations and official dinners, when he was given meeds of praise which were his due. Following his death memorial exercises were held by the Nashville Academy of Medicine and the Tennessee Medical Association.

This recital of beginnings, duties and achievements does not begin to tell the story. It is not an overstatement to say that "Will" Haggard personally knew, and was known by, more medical men than any physician of his day and time. His companionable qualities, together with his regular attendance upon the sessions of the numerous societies which claimed him as a member, brought him into the closest association with his colleagues. A ready response to acquaintance was his gift and he never forgot a name or a face. To meet him was to know him, and to know him was to be attracted to him. He was a friendly friend—gay, genial and generous. Not once did he fail to avow an obligation or to grant a favor. His friendship was of the type that began when first formed, carried on with the same understanding whether contacts were rare or frequent, and blossomed forth in joyous fellowship whenever he communed with his comrades. On the surface there appeared only a care-free manner, a hail-fellow-well-met ardor, but deep down inside there were real affection, loyal love for his "buddies" and strong ties of unwavering cordiality. His intimates were few, but to them he manifested at times a serious vein not unmingled even with heartfelt emotion.

As a man, "Will" Haggard was the life of every company in which he found himself. As expressed by Dr. Joseph F. Gallagher, one of his confreres: "Whether he was among the highest or the lowest of the low, he was, despite his stature, a commanding figure." And further: "His art of conversation linked with a gift of repartee and sense of humor, made an impression not easily forgotten. He loved the beautiful, the elegant, and everything that he attempted was done in the manner grand." In the words of Dr. Frank K. Boland, one of our own Fellows: "Truly he did a lot of living in his 67 years. No man ever had more fun or contributed more pleasure to others, nor has one among us worked harder or given more of himself to his profession and to his patients. He leaves a fine example for posterity of happily rounded, beneficent manhood." He is sorely missed, and he will be missed much more as time goes on, when we meet each year and find his place vacant.

As a surgeon, Doctor Haggard possessed those attributes which make for success. Cheerfulness, courage, and humanity marked every step of his life. He showed sound judgment, a tolerant attitude and a progressive disposition. He learned more and more every year by study and observation, and he kept up, aggressively, with the advances in surgery. He believed in the unity of medicine and his experience made him well-rounded in his views of every situation that confronted him. His operative skill was characterized by resourcefulness and quick thinking, he had by nature a manual dexterity which was as gentle and graceful as it was effective. His one idea was to cure the patient by the safest and simplest method. As a clinical teacher he excelled, what with his aptitude of expression combined with a wealth of illustrations and anecdotes.

The end crowns the work. He always dreaded and feared that, in the

ill-health of his latter days, he would succumb to a lingering disease, which would consign him to a period of chronic invalidism. He wanted to leave this world as his friends knew him, the embodiment of physical activity and irresistible enthusiasm. His wish was fulfilled.

According to a newspaper account Doctor Haggard had recently gone to Florida where he had spent a brief vacation with his two sons just before Christmas, and was with a group of Nashvillians at The Breakers Hotel, Palm Beach. He had dined with them Saturday night and appeared in his usual good health. He did not come down to breakfast Sunday morning and about noon his room was entered and he was discovered dead. Physicians who were called estimated that he had died of a heart attack about seven hours earlier. "He died not too close to the sunset of life, so that the lengthening shadows of his unusual talents and individuality were plain to view and not obscured by the gathering dusk of a falling night of mental darkness. Thus the memory of him by those he loved, and was loved, lives in happy and undying remembrance." (Doctor Gallagher.)

A fitting close for this tribute to our deceased Fellow is contained in a Memoir of his father written in 1901, demonstrating how true to form was the influence of sire upon son. "His only fear in life was of paralysis and a lingering death. He feared that his great physical vigor would postpone the end to a wearying length. He was spared this fear and rewarded with the sudden demise for which he wished—from cerebral hemorrhage."

HUBERT A. ROYSTER M.D.

BOOK REVIEWS

OPERATIVE SURGERY By J. SHELTON HORSLEY, M.D., LL.D., F.A.C.S., Richmond, Va., and ISAAC BIGGER, M.D., Richmond, Va. St. Louis, Mo. C.V. Mosby Co.

THIS is the Fifth Edition of a standard textbook of "Operative Surgery" by Doctors Horsley and Bigger, which was first published in 1921. But three years have elapsed since the appearance of the Fourth Edition, however, no one will take issue with the authors' statement that such rapid progress is now taking place in surgery that a revision at this time was indicated. As in the Fourth Edition, the book appears in two volumes, which are a credit to the publisher and add new laurels to the illustrator, Helen Lorraine.

In the preface one finds outlined the newer procedures which have been added, such as ligation of the patent ductus arteriosus, segmental pneumonectomy, and extrapleural pneumothorax. But this does not speak of the careful reediting which is evident upon almost every page of the book when one compares it with the previous edition.

The chapter on peritonitis has been almost completely rewritten and now occupies 28 pages, and there has been a similar editing of the chapter on appendicitis, which is very greatly expanded.

In this work they still carry a section on orthopedics, which is gradually being deleted from the textbooks on general surgery, and while it maintains its former high standard, the accepted technics of practically all the newer procedures in orthopedic surgery are now included.

The illustrations throughout the entire book maintain the uniform perfection which has been so characteristic of this textbook from its First Edition, and these illustrations are a great asset to those of us who are more visually minded than word minded.

That the authors have accomplished their objective, and have brought this long recognized standard textbook of "Operative Surgery" up to date will be evident to any one fortunate enough to possess a copy.

All concerned in the reediting of this work are to be congratulated upon this addition to our surgical literature.

WALTER ESTELL LEE, M.D.

PRINCIPLES OF SURGICAL CARE, SHOCK AND OTHER PROCEDURES By ALFRED BLALOCK, M.D., Nashville, Tenn. St. Louis, Mo. C.V. Mosby Co., 1940.

THIS MONOGRAPH is an amplification of the Beaumont Lecture, delivered, in 1940, by the author, under the auspices of the Wayne County Medical Society of Michigan, and serves to continue, uninterruptedly, the series of physiologic monographs inaugurated in 1922, as a tribute to William Beaumont.

As stated in the preface, the author's purpose is to present a discussion of the principles involved in these problems instead of a didactic and detailed consideration of the preoperative and postoperative treatment of surgical patients. To the reviewer, he has fully succeeded in his main objective, which was to emphasize the fact that the operation is only a part of the treatment of surgical patients, and that the recent decrease in the morbidity and mortality rates is due more to advances in preoperative and postoperative treatment than to any other factor. A far cry from the epigram credited to Larry "I make the wounds, God heals them."

It is now realized that it is inadequate to discuss the subject of shock without considering such etiologic factors as dehydration, hypoproteinemia, acid-base disturbances, etc., but the clinical importance of these changes extends far beyond the production of shock, so that the amount of text which the author devotes to these etiologic and associated factors is much greater than that given to the subject of shock. The general reference to his many associates removes any possibility of criticism of insularism, and for the final result the surgical and medical professions are under great obligations.

The catholicity of this book is in contrast with the one recently written by Scudder,

and although they are not in complete agreement, they evidence the careful research which has been made, and is continuing, in an effort to make surgery safer for the patient. Here is a book which should not only be in the library of every surgeon and physician, but its contents should become as much a part of them as their knowledge of Gray's Anatomy and Osler's Medicine.

The author and the publisher are to be congratulated, and the Lectureship Foundation Committee of the Wayne County Medical Society thanked for this remarkable work which they have made available to the medical profession at large.

WALTER ESTELL LEE, M D

CANCER OF THE COLON AND RECTUM ITS DIAGNOSIS AND TREATMENT By FRED W RANKIN, M D, Surgeon, St Joseph's and Good Samaritan Hospitals, Lexington, Ky, and A STEPHENS GRAHAM, M D, Surgeon, Stuart Circle Hospital, Richmond, Va. Springfield, Ill. Charles C Thomas Co., 1940

RANKIN AND GRAHAM, in this book, present their experience with cancer of the lower gastro-intestinal tract, and have tried to correlate their work with that of other surgeons interested in this field, both in this country and abroad. They feel that the reduction in mortality from cancer of the large bowel during the last 25 years is one of the most outstanding surgical accomplishments during that period, and undoubtedly Rankin has contributed as much to this result as any other American surgeon of his generation. He himself feels that the gradual decrease in the mortality is the result of more accurate methods of diagnosis, the meticulous preoperative preparation and postoperative care, together with perfection of surgical technic.

Since the publication, in 1932, of his book on "Diseases of the Colon and Rectum," his technic has been modified in many ways, and particularly in the direction of closer cooperation between internist and surgeon in the management of the patient pre- and post-operatively, which has resulted in an appreciation of the need for preoperative decompression of the large bowel and a rehabilitation of the patient before any operative procedure can be considered.

The authors now feel that, in the past, undue prominence was given to the employment of intraperitoneal vaccine, and they have now abandoned it.

They also pay tribute to the increased efficiency of radiology in recognizing early lesions, and in the more accurate localization of them. This is more than lip service, in that he has allotted a chapter to Doctor Hodges, in which is explained, in a very clear, concise way, the details of this technic and what can be expected from it, both positively and negatively.

The authors are very definite in their present attitude toward two-stage instead of a one-stage operation in obstructive lesions of cancer of the middle and lower colon, and they are convinced that one does a more radical operation and removes wider areas of lymph node-bearing tissue than when primary reestablishment of the continuity of the bowel is attempted. Further, in this type of operative approach, they precede it with a cecostomy in order to decompress the colon. On the other hand, for cancer of the rectum, in the average risk, they now use, almost exclusively a one-stage, abdomino-perineal procedure instead of a two-stage operation, which was formerly employed.

Thus it will be seen that Rankin's technic is gradually changing as is that of most of the surgeons engaged in this type of work, and it is interesting to note that there is now more general agreement among them than at any time in the past.

The book is divided into four parts: (1) Preface, (2) general considerations, which include etiology, pathology, symptoms and diagnosis, (3) treatment, and (4) the operative procedures.

With Rankin's vast experience in this field he can speak with authority and his attitude of encouragement toward the steady improvement in the end-results now being obtained in cancer of the large bowel should be noted with interest.

There is a bibliography at the end of each chapter and an authors' and a subject index at the end of the book.

WALTER ESTELL LEE, M D

FINNEY-HOWELL RESEARCH FOUNDATION, INC

Announcement has been made by the Finney-Howell Research Foundation, Inc, that all applications for fellowships for next year must be filed in the office of the Foundation, 1211 Cathedral Street, Baltimore, Maryland, by January 1, 1941. Applications received after that date cannot be considered for 1941 awards, which will be made the first of March, 1941.

This Foundation was provided for in the will of the late Dr. George Walker of Baltimore for the support of "research work into the cause or causes and the treatment of cancer." The will directed that the surplus income from the assets of the Foundation together with the principal sum should be expended within a period of ten years to support a number of fellowships in cancer research, each with an annual stipend of two thousand dollars, "in such universities, laboratories and other institutions, wherever situated, as may be approved by the Board of Directors."

Fellowships carrying an annual stipend of \$2000 are awarded for a period of one year, with the possibility of renewal up to three years, when deemed wise by the Board of Directors, special grants of limited sums may be made to support the work carried on under a fellowship.

Applications must be made on the blank forms which will be furnished by the Secretary or any member of the Board of Directors.

October 15, 1940

EDITORIAL ADDRESS

Original typed manuscripts and illustrations submitted to this Journal should be forwarded prepaid, at the author's risk, to the Chairman of the Editorial Board of the ANNALS OF SURGERY

Walter Estell Lee, M D
1833 Pine Street, Philadelphia, Pa

Contributions in a foreign language when accepted will be translated and published in English

Exchanges and Books for Review should be sent to James T. Pilcher, M D, Managing Editor, 121 Gates Avenue, Brooklyn, N Y

Subscriptions, advertising and all business communications should be addressed

ANNALS OF SURGERY
227 South Sixth Street, Philadelphia, Pa

INDEX TO VOLUME 112

A

- ABBOTT, W OSLER Fluid and Nutritional Maintenance by Use of an Intestinal Tube, 584
- Abdominal Aorta, Aneurysm of, 895, at Its Bifurcation into the Common Iliac Arteries, Aneurysm of the, 909, The Surgical Treatment of Aneurysm of the, 879
- ABELL, IRVIN The Question of Drainage Following Cholecystectomy, 1035
- ABELL, IRVIN, JR The Question of Drainage Following Cholecystectomy, 1035
- Abdominal Neoplasms of Neurogenic Origin, 700
- Absorption of Sulfanilamide from the Large Intestine, 417
- Acidity, Gastric, Before and After Operative Procedure, with Reference to Rôle of the Pylorus and Antrum, 626
- Address of President, 481
- Adenoma of Islets of Langerhans with Hyperinsulinism, Associated with Adenoma of the Thyroid, 378
- Adhesions, Peritoneal, Heparin in the Prevention of, 969
- Air and Carbon Dioxide, Injections of, into a Pulmonary Vein, 212
- Air-Borne Bacterial Contamination, Operative and Postoperative Infections with Reference to, 271
- Allis' Method of Reduction of Posterior Dislocation of the Hip, Improvement to, 127
- Amino-Acids of Hydrolyzed Casein, Parenteral Replacement of Protein with, 594
- Amputations, Leg, in Diabetic Gangrene, 105
- Anastomoses, Surgical, between Biliary and Intestinal Tracts of Children, 51
- ANDRUS, WILLIAM DEW Use of Intramuscular Injections of 2-Methyl-1, 4-Naphthoquinone in Treatment of Prothrombin Deficiencies 783
- Anemic Tissue, Survival of, Effects of Temperature on, 130
- Anesthesia Studies with Photo-Electric Oxyhemoglobinograph, 791
- Aneurysm of the Abdominal Aorta, The Surgical Treatment of, 879
- Angiomata of the Lower Extremities Associated with Varicose Veins, Circulatory Disturbances Produced by, 960
- Anomalies, Congenital, of the Duodenum, 321
- Anus, Congenital Pedunculated Pseudopapilloma of, 297
- Aorta, Abdominal, Aneurysm of the, 895, at Its Bifurcation into the Common Iliac Arteries, Aneurysm of the, 909, Surgical Treatment of Aneurysm of the, 879
- ARNHEIM, ERNEST E Diverticulitis of the

Colon with Reference to Surgical Complications, 352

- ARONSON, SHEPARD G Acute Cholecystitis Preceding Neoplastic Common Bile Duct Obstruction, 400
- Arteries, Iliac, Aneurysm of the Abdominal Aorta at Its Bifurcation into the Common, 909, Large, Experimental Studies on the Gradual Occlusion of 923
- Arteriovenous Fistulae, Clinical and Experimental Observations on, 840
- Attachment, Locking, for Balfour Retractor, 310

B

- Bacterial Contamination, Air-Borne, Operative and Postoperative Infections with Reference to, 271
- BAKER, CHARLES P Studies Relating to the Pathogenesis of Cholecystitis, Cholelithiasis and Acute Pancreatitis, 1006
- Balfour Retractor, Locking Attachment for, 310
- BATSON, OSCAR V Function of Vertebral Veins and Their Rôle in Spread of Metastases, 138
- BELL, H GLENN Surgical Management of Carcinoma of Left Half of Colon, 763
- BELLAS, JOSEPH E Influence of Sutures Upon Operative Wounds, 112
- Benign Tumors of the Bronchi, Thoracic Broncotomy for Removal of, 1067
- BERGER, R A Leiomyosarcoma of the Stomach, 22
- BIGGER, I A The Surgical Treatment of Aneurysm of the Abdominal Aorta, 879
- Bilateral and Bilocular Empyema, 426
- Bile Duct, Common, Exploration of, 64, Obstruction, Neoplastic Common, Acute Cholecystitis Preceding, 400
- Biliary and Intestinal Tracts of Children, Surgical Anastomoses between, 51
- BISGARD, DEWEY J Studies Relating to the Pathogenesis of Cholecystitis, Cholelithiasis and Acute Pancreatitis, 1006
- BLAIR, VILRAY P Toe to Finger Transplant, 287
- BLALOCK, ALFRED Plasma Loss in Severe Dehydration, Shock and Other Conditions as Affected by Therapy, 557
- Blood, Preservation of, 498, Studies in, 502
- Blood Stream Invasion, Suppurative Thrombophlebitis of Femoro-Iliac Vein with, 294
- Blood, Structure of, in Relation to Surgical Problems, 490
- Bone, Metastatic Pulsating Tumor of, Secondary to Renal Carcinoma, 249

BOOK REVIEW Cancer of the Colon and Rectum Its Diagnosis and Treatment, by Fred W Rankin, MD and A Stephens Graham, MD, Reviewed by Walter E Lee, 1135, Diverticula and Diverticulitis of the Intestine, by Harold C Edwards, Reviewed by Carl Eggers, 315, "Harvey Cushing's Seventieth Birthday Party," Reviewed by Walter E Lee, 313, Operative Surgery, by J Shelton Horsley, MD and Isaac Bigger, MD, Reviewed by Walter E Lee, 1134, Principles of Surgical Care, Shock and Other Procedures, by Alfred Blalock, MD, Reviewed by Walter E Lee, 1134, Shock, Blood Studies as a Guide to Therapy, by John Scudder, Reviewed by James L Gamble, 314, Treatment of War Wounds and Fractures, by J Trueta, Reviewed by Walter E Lee, 311

BOYS, FLOYD Heparin in the Prevention of Peritoneal Adhesions, 969

BRASELTON, C W, JR, Injections of Air and Carbon Dioxide into a Pulmonary Vein, 212

Bronchi, Transthoracic Bronchotomy for Removal of Benign Tumors of the, 1067

Bronchotomy for Removal of Benign Tumors of the Bronchi, 1067

BROOKS, BARNEY Effects of Temperature on Survival of Anemic Tissue, 130

BRUECKEN, A J Adenoma of Islets of Langerhans with Hyperinsulinism, Associated with Adenoma of Thyroid, 378

BULL, DAVID C Preservation of Blood 498

Burn, Irradiation, of the Intestine, 769

Burns, Severe, Fluid Shift in, Plasma Transfusion in Treatment of, 150, Liver Damage and Dextrose Tolerance in, 158

BYARS, LOUIS T Toe to Finger Transplant, 287

C

Canal, Femoral, The Repair of Inguinal Hernia with Transplantation of the Cord to the, 1071

Capitellum, Fracture of the, 122

Carbon Dioxide and Air, Injections of, into a Pulmonary Vein, 212

Carcinoma of Left Half of Colon Surgical Management of, 763, of the Stomach, Total Gastrectomy for, 31, of the Thyroid, 977, Renal, Metastatic Pulsating Tumor of Bone Secondary to, 249

Cartilage, Semilunar, Cyst of the, 305

Casein, Hydrolyzed, Parenteral Replacement of Protein with Amino-Acids of, 594

Catgut Ligatures and Knots, Physical Factors of, 471

CAVE HENRY W Ileostomy, 747

CAYLOR, HAROLD D Locking Attachment for Balfour Retractor, 310

Chemical Section of the Cervicodorsal and Lumbar Sympathetics in the Prevention of Ischemic Gangrene Following Surgical

Operations upon the Major Peripheral Arteries, 938

Children, Biliary and Intestinal Tracts, Surgical Anastomoses between, 51

Cholecystectomy, The Question of Drainage Following, 1035

Cholecystitis, Cholelithiasis and Acute Pancreatitis, Pathogenesis of and Studies Relating to the, 1006, Acute, Preceding Neoplastic Common Bile Duct Obstruction, 400

Cholelithiasis, Cholecystitis, and Acute Pancreatitis, Pathogenesis of and Studies Relating to the, 1006

Civilian Medical Officers, Government's Need of Temporary and Part-Time, 801

Cleft Palate Surgery, Experiences in, 775

Clinical Study of Plasma Volume in Acute Intestinal Obstruction, 546

Closure, Delayed, of Contaminated Wounds, 256

COLCOCK, BINTLEY P Diagnosis and Surgical Management of Leiomyomata and Leiomyosarcomata of the Stomach, 671

COLLY, BRADLEY L Factors Influencing the Prognosis in Osteogenic Sarcoma, 1114

COLLER, FRIDRICK A Delayed Closure of Contaminated Wounds, 256, Sodium Chloride Metabolism of Surgical Patients, 520

Colon, Carcinoma of Left Half of, Surgical Management of, 763, Diverticulitis of the, with Reference to Surgical Complications, 352

Colonmetrogram, Neurogenic Disturbances of the Colon and Their Investigation by the, 1042

Colostomy, Divine, A Duraluminum Enterotome for, 975

Common Bile Duct, Exploration of 64, Obstruction, Neoplastic, Acute Cholecystitis Preceding, 400

Complications, Surgical, Diverticulitis of the Colon, with Reference to, 352

Congenital Anomalies of the Duodenum, 321, Hemolytic Jaundice, 392, Pedunculated Pseudopapilloma of Anus, 297, Pyloric Stenosis, 687

Contaminated Wounds, Delayed Closure of, 256

Contamination, Air-Borne Bacterial, Operative and Postoperative Infections with Reference to, 271

Critical Latent or Lag Period in Healing of Wounds, 481

Cyst, Enterogenous, 300, of the Semilunar Cartilage, 305

Cysts of the Mesentery, 80

D

Damage, Liver, and Dextrose Tolerance in Severe Burns, 158

DARRACH, WILLIAM Obituary of George E Brewer, 795

- DAVIS, LINCOLN Obituary of George W W Brewster, by, 319
- DAVIS, LOYAL The Early Symptoms and Treatment of Nasopharyngeal Tumors, 1058
- DE YOE, LEON, E Suggested Improvement to Allis Method of Reduction of Posterior Dislocation of Hip, 127
- Dehydration, Severe, Shock and Other Conditions as Affected by Therapy, Plasma Loss in 557
- Delayed Closure of Contaminated Wounds, 256
- Denervation, Sympathetic, of The Upper Extremity by Preganglionic Section, the Problem of Producing Complete and Lasting, 1085
- Derangements Internal of Knee Joint, 454
- Dextrose Tolerance and Liver Damage in Severe Burns 158
- Diabetes and Pancreatitis, Acute, 177
- Diabetic Gangrene, Leg Amputations in, 105
- Diagnosis and Surgical Management of Leiomyomata and Leiomyosarcomata of the Stomach, 671, Treatment of Gastric Lesions, 339
- Dislocation, Posterior, of the Hip, Reduction of, Improvement to Allis' Method of, 127
- Disturbances of the Colon and Their Investigation by the Colonmetrogram, Neurogenic, 1042, Produced by Extensive Angiomata of the Lower Extremities Associated with Varicose Veins, 960
- Diverticulitis of the Colon with Reference to Surgical Complications, 352
- Drainage Following Cholecystectomy, The Question of, 1035, Intestinal Suction, Fluid, Salt and Nutritional Balance in Patients with, 530
- DREW, CHARLES R Preservation of Blood, 498
- DUNCAN, GEORGE W Effects of Temperature on Survival of Anemic Tissue, 130
- Duodenal Obstruction in Infancy, Ladd's Operation for Cure of Incomplete Rotation and Volvulus of Small Intestine Producing 234
- Duodenum, Congenital Anomalies of the, 321
- E**
- Effects of Temperature on Survival of Anemic Tissue, 130
- EGGERS, CARL Review of Diverticula and Diverticulitis of the Intestine, by, 315
- EHLER, ADRIAN A Bilateral and Bilocular Empyema, 426
- EHRENTHEIL, OTTO Neurogenic Disturbances of the Colon and Their Investigation by the Colonmetrogram, 1042
- Electrosurgical Excision of Subesophageal Chronic Penetrating or Perforated Gastric Ulcer, 219
- ELKIN, DANIEL C Aneurysm of the Abdominal Aorta Treatment by Ligation, 895, Wound Infection, 280
- ELKINTON, J RUSSELL Liver Damage and Dextrose Tolerance in Severe Burns, 158, Plasma Transfusion in Treatment of Fluid Shift in Severe Burns, 150
- ELMAN, ROBERT Ladd's Operation for Cure of Incomplete Rotation and Volvulus of Small Intestine Producing Duodenal Obstruction in Infancy, 234, Parenteral Replacement of Protein with Amino-Acids of Hydrolyzed Casein, 594
- ELOESSER, LEO Transthoracic Bronchotomy for Removal of Benign Tumors of the Bronchi, 1067
- Empyema, Bilateral and Bilocular, 426
- Enteric Intussusception Retrograde, 344
- Enterogenous Cyst, 300
- Enterotome, Duraluminum, for Devine Colostomy, 975
- ERRATUM Correction in article by Charles H Watt, M D, "A Modified Spur-Crushing Clamp and Its Use" ANNALS OF SURGERY, 111, 1076-1083, June, 1940, 160
- Essential Hypertension, a Rôle for Surgeons in the Problem of, 1101
- Evaluation of Original Serologic Tests for Syphilis, 480
- Excision, Electrosurgical, of Subesophageal, Chronic Penetrating or Perforated Gastric Ulcer 219
- Experiences in Cleft Palate Surgery, 775, Vascular Surgery, Personal, 802
- Experimental Intestinal Obstruction, Plasma Transfusion in, 240, Observations on Arteriovenous Fistulae, Clinical and 840
- Exploration of Common Bile Duct, 64
- Extensive Angiomata of the Lower Extremities Associated with Varicose Veins, Circulatory Disturbances Produced by, 960
- Extremities, Lower, Circulatory Disturbances Produced by Extensive Angiomata of the, and Associated with Varicose Veins, 960
- F**
- Factors, Physical, of Catgut Ligatures and Knots, 471, Physiologic, Regulating Level of Plasma Prothrombin, 568
- Febrile Reactions, Relation of Proper Preparation of Solutions for Intravenous Therapy to, 603
- Femoral Canal, the Repair of Inguinal Hernia with Transplantation of the Cord to the, 1071
- Femoro-Iliac Vein, Suppurative Thrombophlebitis of, with Blood Stream Invasion, 294
- FERGUSON, L KRAEER Internal Derangements of Knee Joint, 454
- FINE, JACOB Clinical Study of Plasma Volume in Acute Intestinal Obstruction,

- 546, Plasma Transfusion in Experimental Intestinal Obstruction, 240
Finger, Missing, Transplantation of Toe for, 291, Toe to, Transplant of, 287
Finney-Howell Research Foundation, Inc., Notice of, 1136
Fistulae, Arteriovenous Clinical and Experimental Observations on, 840
Fluid, Salt and Nutritional Balance in Patients with Intestinal Suction Drainage, 530, Shift in Severe Burns, Plasma Transfusion in Treatment of, 150, and Nutritional Maintenance by Use of an Intestinal Tube, 584
FORSTER, ARMAND C Production of Hyper- and Hypomotility of Musculature of Small Bowel in the Human, 370
Fracture of the Capitellum, 122
FRANCONA, NICHOLAS T Tuberculosis of the Stomach, 225
FRANTZ, V KNEELAND Tumors of Islet Cells with Hyperinsulinism, 161
FREFMAN, NORMAN E Circulatory Disturbances Produced by Extensive Angiomata of the Lower Extremities Associated with Varicose Veins, 960
Function of Vertebral Veins and Their Role in Spread of Metastases, 138

G

- GAGE, MIMS A Dualuminum Enterotome for Devine Colostomy, 975, The Prevention of Ischemic Gangrene Following Surgical Operations upon the Major Peripheral Arteries by Chemical Section of the Cervicodorsal and Lumbar Sympathetics, 938
GAMBLE, JAMES L Review of Shock, Blood Studies as a Guide to Therapy, by, 314
Gangrene, Diabetic, Leg Amputations in 105, Ischemic, Prevention of, Following Surgical Operations upon the Major Peripheral Arteries by Chemical Section of the Cervicodorsal and Lumbar Sympathetics, 938
Gastrectomy, Total, for Carcinoma of the Stomach 31
Gastric Acidity Before and After Operative Procedure with Reference to Role of the Pylorus and Antrum, 626, Lesions, Diagnosis and Treatment of, 339, Ulcer, Subesophageal Chronic Penetrating or Perforated, Electrosurgical Excision of, 219
Gastro-Intestinal Tract, Perforations of the, 37
GENDEL SAMUEL Plasma Transfusion in Experimental Intestinal Obstruction, 240
GLENN, FRANK Exploration of Common Bile Duct, 64
Government's Need of Temporary and Part-Time Civilian Medical Officers 801
Graduate Teaching of Surgical Pathology, 284
GRANT, EMIL Treatment of Perianal Tuberculosis, 440
GREEN, WARREN W Congenital, Pedunculated Pseudopapilloma of Anus, 297
GREENLEE, D P Adenoma of Islets of Langerhans, with Hyperinsulinism Associated with Adenoma of Thyroid, 378
GROPER, MORRIS J Retrograde Enteric Intussusception, 344
GROSS, ROBERT E Surgical Anastomoses between Biliary and Gastro-Intestinal Tracts of Children, 51

H

- HARF, HUGH F Carcinoma of the Thyroid, 977
Hare's Syndrome in Relation to Tumor of Pancoast, 1
HARKEN, DWIGHT E Superior Pulmonary Sulcus, Tumor of Pancoast, in Relation to Hare's Syndrome, 1
HARTMAN, FRANK W Further Anesthesia Studies with Photo-Electric Oxyhemoglobinograph, 791
Hashimoto (Struma Lymphomatosa), 421
HAY, LILI Gastric Acidity Before and After Operative Procedure with Reference to Role of the Pylorus and Antrum, 626
Healing of Wounds, Critical Latent or Lag Period in, 481
HILNBCKER, PETIR A Role for Surgeons in the Problem of Essential Hypertension, 1101
Hemolytic Jaundice, Congenital, 392
Hernia, Inguinal, the Repair of, with Transplantation of the Cord to the Femoral Canal, 1071
Hip, Reduction of Posterior Dislocation of, Improvement to Allis' Method of, 127
HOLMAN, CRANSTON W Further Observations on Diagnosis and Treatment of Gastric Lesions, 339
HOLMAN, EMILE Clinical and Experimental Observations on Arteriovenous Fistulae, 840
HORINF, CYRUS F Some Physical Factors of Catgut Ligatures and Knots, 471
HORSLEY, GUY W Leiomyosarcoma of the Stomach, 22
HOUSER, MILES S Locking Attachment for Balfour Retractor 310
HURLEY, ANSON G Congenital Hemolytic Jaundice, 392
HURWITZ, ALFRED Clinical Study of Plasma Volume in Acute Intestinal Obstruction 546
Hydrolyzed Casein, Parenteral Replacement of Protein with Amino-Acids of, 594
Hyper- and Hypomotility of Musculature of Small Bowel in the Human, 370
Hyperinsulinism, Adenoma of Islets of Langerhans with, Associated with Adenoma of the Thyroid, 378, Tumors of Islet Cells with, 161
Hypertension, Essential A Role for Surgeons in the Problem of, 1101

Hypoproteinemia and Its Relation to Surgical Problems, 576

I

- Ileostomy, 747
 Iliac, Arteries, Aneurysm of the Abdominal Aorta at Its Bifurcation into the Common, 909
 Improvement to Allis' Method of Reduction of Posterior Dislocation of the Hip, 127
 Incomplete Rotation and Volvulus of Small Intestine, Ladd's Operation for Cure of, Producing Duodenal Obstruction in Infancy, 234
 Infancy, Duodenal Obstruction in, Ladd's Operation for Cure of Incomplete Rotation and Volvulus of Small Intestine, Producing, 234
 Infection, Wound, 280
 Infections, Operative and Postoperative with Reference to Air-Borne Bacterial Contamination, 271
 Influence of Sutures Upon Operative Wounds, 112
 Inguinal hernia with Transplantation of the Cord to the Femoral Canal, the Repair of, 1071
 Injections of Air and Carbon Dioxide into a Pulmonary Vein, 212
 Internal Derangements of Knee Joint, 454
 Intestinal Obstruction, Acute, Clinical Study of Plasma Volume in, 546, Obstruction, Experimental, Plasma Transfusion in 240, Suction Drainage, Fluid, Salt and Nutritional Balance in Patients with, 530, Tube, Fluid and Nutritional Maintenance by Use of an, 584, and Biliary Tracts of Children, Surgical Anastomoses between, 51
 Intestine, Irradiation Burn of the, 769, Large, Absorption of Sulfanilamide from, 417
 Intramuscular Injections of 2-Methyl-1, 4-Naphthoquinone in Treatment of Prothrombin Deficiencies, 783
 Intravenous Therapy to Febrile Reactions, Relation of Proper Preparation of Solutions for, 603
 Intussusception, Retrograde Enteric, 344
 Irradiation Burn of the Intestine, 769
 IRVIN, J LOGAN Fluid, Salt and Nutritional Balance in Patients with Intestinal Suction Drainage, 530
 Ischemic Gangrene, Prevention of Following Surgical Operations upon the Major Peripheral Arteries by Chemical Section of the Cervicodorsal and Lumbar Sympathetics, 938
 Islet Cells, Tumors of, with Hyperinsulinism, 161
 Islets of Langerhans, Adenoma of, with Hyperinsulinism, Associated with Adenoma of the Thyroid, 378
 IYI, ROBERT H Experiences in Cleft Palate Surgery, 775

J

- JACKSON, REGINALD H Electrosurgical Excision of Subesophageal, Chronic Penetrating or Perforated Gastric Ulcer, 219
 Jaundice, Congenital Hemolytic, 392

K

- KAY, EARLE B Abdominal Neoplasms of Neurogenic Origin, 700
 KEARNS, J E, JR Struma Lymphomatosa (Hashimoto), 421
 KIRSHBAUM, JACK D Tuberculosis of the Stomach, 225
 Knee Joint, Internal Derangements of, 454
 Knots and Ligatures, Catgut, Physical Factors of, 471

L

- LADD, WILLIAM E Surgical Anastomoses between Biliary and Gastro-Intestinal Tracts of Children, 51
 Ladd's Operation for Cure of Incomplete Rotation and Volvulus of Small Intestine, Producing Duodenal Obstruction in Infancy, 234
 LAHEY, FRANK H Carcinoma of the Thyroid, 977, Diagnosis and Surgical Management of Leiomyomata and Leiomyosarcomata of the Stomach, 671
 Langerhans, Adenoma of Islets of, with Hyperinsulinism, Associated with Adenoma of the Thyroid, 378
 Large Intestine, Absorption of Sulfanilamide from, 417
 LEE, WALTER ESTELL Circulatory Disturbances Produced by Extensive Angiomata of the Lower Extremities Associated with Varicose Veins, 960, Plasma Transfusion in Treatment of Fluid Shift in Severe Burns, 150, Review of Cancer of the Colon and Rectum Its Diagnosis and Treatment, by, 1135, Review of "Harvey Cushing's Seventieth Birthday Party," 313, Review of Operative Surgery, by, 1134, Review of Principles of Surgical Care, Shock and Other Procedures, by, 1134, Review of Treatment of War Wounds and Fractures, by, 311
 Left Half of Colon, Carcinoma of, Surgical Management of, 763
 Leg Amputations in Diabetic Gangrene, 105
 LEHMAN, EDWIN P Heparin in the Prevention of Peritoneal Adhesions, 969
 Leiomyomata and Leiomyosarcomata of the Stomach, Diagnosis and Surgical Management of, 671
 Leiomyosarcoma of the Stomach, 22
 LEMMON, WILLIAM T Total Gastrectomy for Carcinoma of the Stomach, 31
 Leukoplakic Vulvitis, 87
 Level of Plasma Prothrombin, Physiologic Factors Regulating the, 568

Ligation of Aneurysm of the Abdominal Aorta, Treatment by, 895
Ligatures and Knots, Catgut, Physical Factors of, 471
LINDNER, HAROLD H Congenital Anomalies of the Duodenum, 321
Liver Damage and Dextrose Tolerance in Severe Burns, 158
LLOYD, J G Adenoma of Islets of Langerhans with Hyperinsulinism, Associated with Adenoma of Thyroid, 378
Lobectomy and Pneumonectomy in Pulmonary Tuberculosis, 201
Locking Attachment for Balfour Retractor, 310
LORD, JEFF W, JR Use of Intramuscular Injections of 2-Methyl-1, 2-Naphthoquinone in Treatment of Prothrombin Deficiencies, 783
LOWER, WILLIAM E Ureteral Transplantation, 100
Lymphomatosa, Struma (Hashimoto), 421

M

MACFEE, WILLIAM F The Repair of Inguinal Hernia with Transplantation of the Cord to the Femoral Canal, 1071
MADDOCK, WALTER G Sodium Chloride Metabolism of Surgical Patients, 520
MAGATH, THOMAS B Operative and Post-operative Infections with Reference to Air-Borne Bacterial Contamination, 271
Maintenance, Fluid and Nutritional, by Use of an Intestinal Tube, 584
Major Peripheral Arteries, Surgical Operations upon the Prevention of Ischemic Gangrene Following Chemical Section of the Cervicodorsal and Lumbar Sympathetics, 938
Management, Surgical, and Diagnosis of Leiomyomata and Leiomyosarcomata of the Stomach, 671, of Carcinoma of Left Half of the Colon, 763
MARINO, A W MARTIN Studies on Absorption of Sulfanilamide from Large Intestine, 417
MARK, JEROME Clinical Study of Plasma Volume in Acute Intestinal Obstruction, 546
MARTIN, JOHN The Early Symptoms and Treatment of Nasopharyngeal Tumors, 1058
MATAS, RUDOLPH Aneurysm of the Abdominal Aorta at Its Bifurcation into the Common Iliac Arteries, 909, Personal Experiences in Vascular Surgery, 802
McCLURE, ROY D Further Anesthesia Studies with Photo-Electric Oxymoglobinograph, 791
McELROY, W S Adenoma of Islets of Langerhans, with Hyperinsulinism, Associated with Adenoma of Thyroid, 378
McLAUGHLIN, EDWARD F Fracture of the Capitellum, 122
Medical Officers, Civilian Government's Need of Temporary and Part-Time, 801

Mesentery, Cysts of the, 80
Metabolism, Sodium Chloride, of Surgical Patients, 520
Metastases, Spread of, Function of Vertebral Veins and Their Role in, 138
Metastatic Pulsating Tumor of Bone Secondary to Renal Carcinoma, 249
MLYER, HERBERT WILLY Perforations of the Gastro-Intestinal Tract, 37
MINOT, A S Plasma Loss in Severe Dehydration, Shock and Other Conditions as Affected by Therapy, 557
MOORE, R M Injections of Air and Carbon Dioxide into a Pulmonary Vein, 212
MOORE, WILL C Congenital Hemolytic Jaundice, 392
MORRIS, JOHN H Superior Pulmonary Sulcus, Tumor of Pancoast, in Relation to Hare's Syndrome, 1
Musculature of Small Bowel in the Human, Hyper- and Hypomotility of, 370

N

NATFINGER, HOWARD C Surgical Management of Carcinoma of Left Half of the Colon, 763
Nasopharyngeal Tumors, Early Symptoms and Treatment of, 1058
Neoplasms, Abdominal, of Neurogenic Origin, 700
Neoplastic Common Bile Duct Obstruction, Acute Cholecystitis Preceding, 400
NERB, LOUIS Studies on Absorption of Sulfanilamide from Large Intestine, 417
NEUBOR, HAROLD Transplantation of Toe for Missing Finger, 291
Neurogenic Disturbances of the Colon and Their Investigation by the Colonmetrogram, 1042, Origin, Abdominal Neoplasms of, 700
NICHOLSON, JESSE T Cyst of the Semilunar Cartilage, 305
NICKEL, WILLIAM F, JR Ileostomy, 747
Nutritional Balance, Fluid and Salt, in Patients with Intestinal Suction Drainage, 530, and Fluid Maintenance by Use of an Intestinal Tube, 584

O

OBITUARY Brewer, George E, by William Darrach, 795, Brewster, George W W, by Lincoln Davis, 319, Haggard, William David, by Hubert M Royster, 1129, McGlannan, Alexis, by Walter D Wise, 798
Observations on Arteriovenous Fistulae, Clinical and Experimental, 840
Obstruction, Acute Intestinal, Clinical Study of Plasma Volume in, 546 Experimental Intestinal, Plasma Transfusion in, 240
Occlusion, Gradual, of Large Arteries, Experimental Studies on the, 923, Neoplastic Common Bile Duct, Acute Cholecystitis Preceding, 400

- OCHSNER, ALTON The Prevention of Ischemic Gangrene Following Surgical Operations upon the Major Peripheral Arteries by Chemical Section of the Cervicodorsal and Lumbar Sympathetics, 938
- Operative Procedure, Gastric Acidity Before and After, with Reference to Role of the Pylorus and Antrum, 626, Wounds, Influence of Sutures Upon, 112, and Postoperative Infections with Reference to Air-Borne Bacterial Contamination, 271
- Osteogenic Sarcoma, Factors Influencing the Prognosis of 1114
- Oxyhemoglobinograph, Anesthesia Studies with Photo-Electric, 791

P

- Pancoast Tumor of, 1
- Pancreatitis Acute Cholecystitis, Cholelithiasis, Pathogenesis of and Studies Relating to the, 1006, and Diabetes, Acute, 177
- Parenteral Replacement of Protein with Amino-Acids of Hydrolyzed Casein, 594
- PARRAN, THOMAS Announcement of a Study to Evaluate Original Serologic Tests for Syphilis, 480
- PASCHAL, GEORGE W., JR Total Gastrectomy for Carcinoma of the Stomach 31
- Pathogenesis of Cholecystitis, Cholelithiasis and Acute Pancreatitis, Studies Relating to the, 1006
- Pathology, Surgical, Graduate Teaching of, 284
- Patients, Surgical, Sodium Chloride Metabolism of, 520
- PEARSE, HERMAN E Experimental Studies on the Gradual Occlusion of Large Arteries, 923
- Pedunculated Pseudopapilloma of Anus, Congenital, 297
- PENBERTH, GROVER C Fluid, Salt and Nutritional Balance in Patients with Intestinal Suction Drainage, 530
- Perforations of the Gastro-Intestinal Tract, 37
- Perianal Tuberculosis, Treatment of, 440
- Peritoneal Adhesions, Heparin in the Prevention of, 969
- PETERS, JOHN P Structure of Blood in Relation to Surgical Problems, 490
- PETERSON, EDWARD W Cysts of the Mesentery, 80
- Photo-Electric Oxyhemoglobinograph, Anesthesia Studies with 791
- Physical Factors of Catgut Ligatures and Knots, 471
- Physiologic Factors Regulating Level of Plasma Prothrombin, 568
- Plasma Loss in Severe Dehydration, Shock and Other Conditions as Affected by Therapy, 557, Prothrombin, Physiologic Factors Regulating the Level of, 568, Transfusion in Experimental Intestinal

- Obstruction, 240, Transfusion in Treatment of Fluid Shift in Severe Burns, 150, Volume, Clinical Study of, in Acute Intestinal Obstruction, 546
- Pneumonectomy and Lobectomy in Pulmonary Tuberculosis, 201
- POOL, JOHN L Factors Influencing the Prognosis in Osteogenic Sarcoma, 1114
- Posterior Dislocation of the Hip, Reduction of, Improvement to Allis' Method of, 127
- Postoperative and Operative Infections with Reference to Air-Borne Bacterial Contamination 271
- Preganglionic Section, The Problem of Producing Complete and Lasting Sympathetic Denervation of the Upper Extremity by, 1085
- Preparation of Solutions, Relation of Proper, for Intravenous Therapy to Febrile Reactions, 603
- Preservation of Blood, 498
- Preservation, Studies in Blood, 502
- Presidential Address, 481
- Prevention of Peritoneal Adhesions, Heparin in the, 969
- Problems, Surgical, Hypoproteinemia and Its Relation to, 576, Structure of Blood in Relation to, 490
- Prognosis in Osteogenic Sarcoma, Factors Influencing the, 1114
- Protein, Parenteral Replacement of, with Amino-Acids of Hydrolyzed Casein, 594
- Prothrombin Deficiencies, Treatment of, Use of Intramuscular Injections of 2-Methyl-1, 4-Naphthoquinone in, 783, Plasma, Physiologic Factors Regulating the Level of, 568
- Pseudopapilloma of Anus, Congenital, Pedunculated, 297
- Pulmonary Sulcus, Superior, 1, Vein, Injections of Air and Carbon Dioxide into a, 212
- Pulsating Tumor, Metastatic, of Bone Secondary to Renal Carcinoma, 249
- Pyloric Stenosis, Congenital, 687

R

- RANSOM, HENRY K Abdominal Neoplasms of Neurogenic Origin, 700
- RAVDIN, I S Hypoproteinemia and Its Relation to Surgical Problems, 576
- REA, CHARLES E Enterogenous Cyst, 300
- Reduction of Posterior Dislocation of the Hip, Improvement to Allis' Method of, 127
- Relation of Proper Preparation of Solutions for Intravenous Therapy to Febrile Reactions, 603
- Renal Carcinoma, Metastatic Pulsating Tumor of Bone Secondary to, 249
- Repair of Inguinal Hernia with Transplantation of the Cord to the Femoral Canal, 1071
- Replacement Parenteral, of Protein with Amino-Acids of Hydrolyzed Casein, 594

Retractor, Balfour, Locking Attachment for, 310
 Retrograde Enteric Intussusception, 344
 RHODES, JONATHAN E Liver Damage and Dextrose Tolerance in Severe Burns, 158, Physiologic Factors Regulating Level of Plasma Prothrombin, 568
 ROBERTSON, DAVID E Congenital Pyloric Stenosis, 687
 Rotation, Incomplete, and Volvulus of Small Intestine, Ladd's Operation for Cure of, Producing Duodenal Obstruction in Infancy, 234
 ROTHENBERG, ROBERT E Acute Cholecystitis Preceding Neoplastic Common Bile Duct Obstruction, 400
 ROYSTER, HUBERT M Obituary of Wm David Haggard, 1129

S

Salt Fluid and Nutritional Balance in Patients with Intestinal Suction Drainage, 530
 SAMSON, PAUL C Indications for Lobectomy and Pneumonectomy in Pulmonary Tuberculosis, 201
 SAMUELS, SAUL S Leg Amputations in Diabetic Gangrene, 105
 SANDUSKY, WILLIAM R Further Observations on Diagnosis and Treatment of Gastric Lesions, 339
 Sarcoma, Osteogenic, Factors Influencing the Prognosis of, 1114
 SCUDDER, JOHN Studies in Blood Preservation, 502
 Semilunar Cartilage, Cyst of the, 305
 Serologic Tests for Syphilis, Study to Evaluate Original, 480
 SHIH, H E Metastatic Pulsating Tumor of Bone Secondary to Renal Carcinoma, 249
 Shock, Severe Dehydration and Other Conditions as Affected by Therapy, Plasma Loss in, 557
 SHUMACKER, HARRIS B Acute Pancreatitis and Diabetes 177
 Small Bowel in the Human, Hyper- and Hypomotility of Musculature of the, 370
 Small Intestine, Volvulus of, and Incomplete Rotation of, Ladd's Operation for Cure of, Producing Duodenal Obstruction in Infancy, 234
 SMITHWICK, REGINALD H The Problem of Producing Complete and Lasting Sympathetic Denervation of the Upper Extremity by Pre-Ganglionic Section, 1085
 Sodium Chloride Metabolism of Surgical Patients, 520
 Solutions, Relation of Proper Preparation

of, for Intravenous Therapy to Febrile Reactions, 603
 SOMMER, GEORGE N J, JR Bilateral and Bilocular Empyema, 426
 SPARROW, THOMAS D Leukoplakic Vulvitis, 87
 Spread of Metastases, Function of Vertebral Veins and Their Role in, 138
 Stenosis, Congenital Pyloric, 687
 Stomach, Carcinoma of the, Total Gastrectomy for, 31, Leiomyomata and Leiomyosarcomata of the Diagnosis and Surgical Management of, 671, Leiomyosarcoma of the, 22, Tuberculosis of the, 225
 STOUT, ARTHUR PURDY Graduate Teaching of Surgical Pathology, 284
 Structure of Blood in Relation to Surgical Problems, 490
 Struma Lymphomatosa (Hashimoto), 421
 Studies, Anesthesia, with Photo-Electric Oxymyoglobinograph, 791, in Blood Preservation, 502, Relating to the Pathogenesis of Cholecystitis, Cholelithiasis and Acute Pancreatitis, 1006
 Study, Clinical, of Plasma Volume in Acute Intestinal Obstruction, 546
 Subesophageal, Chronic Penetrating or Perforated Gastric Ulcer, Electrosurgical Excision of, 219
 Sulcus, Superior Pulmonary, 1
 Sulfanilamide from Large Intestine, Absorption of, 417
 SULLIVAN, RALPH C Tuberculosis of the Stomach, 225
 Suppurative Thrombophlebitis of Femoro-Iliac Vein with Blood Stream Invasion, 294
 Surgery, Experiences in Cleft Palate, 775, Vascular, Personal Experiences in, 802
 Surgical Anastomoses between Biliary and Intestinal Tracts of Children, 51, Complications, Diverticulitis of the Colon, with Reference to, 352, Management of Carcinoma of Left Half of the Colon 763, Management and Diagnosis of Leiomyomata and Leiomyosarcomata of the Stomach, 671, Pathology, Graduate Teaching of, 284, Patients, Sodium Chloride Metabolism of, 520, Problems, Hypoproteinemia and Its Relation to, 576 Problems, Structure of Blood in Relation to, 490
 Survival of Anemic Tissue, Effects of Temperature on 130
 Sutures, Influence of, upon Operative Wounds, 112
 Sympathetic Denervation of the Upper Extremity by Preganglionic Section, the Problem of Producing Complete and Lasting, 1085

Symptoms, Early, and Treatment of Nasopharyngeal Tumors, 1058
Syphilis, Serologic Tests for, Study to Evaluate Original, 480

T

Teaching, Graduate, of Surgical Pathology, 284
Temperature, Effects of, on Survival of Anemic Tissue, 130
TENERY, R MAYO Fluid, Salt and Nutritional Balance in Patients with Intestinal Suction Drainage, 530
THOMPSON, WESLEY D Internal Derangements of Knee Joint, 454
Thrombophlebitis, Suppurative, of Femoro-Iliac Vein with Blood Stream Invasion, 294
Thyroid, Adenoma of the, Associated with Adenoma of Islets of Langerhans with Hyperinsulinism, 378, Carcinoma of, 977
Toe to Finger Transplant, 287, Transplantation of, for Missing Finger, 291
Total Gastrectomy for Carcinoma of the Stomach, 31
TRACH, BENEDICT Gastric Acidity Before and After Operative Procedure with Reference to Role of the Pylorus and Antrum, 626
Tract, Gastro-Intestinal, Perforations of the, 37
Transfusion, Plasma, in Experimental Intestinal Obstruction, 240, in Treatment of Fluid Shift in Severe Burns, 150
Transplant, Toe to Finger, 287
Transplantation of Toe for Missing Finger, 291, Ureteral, 100
Treatment by Ligation, Aneurysm of the Abdominal Aorta, 895, of Aneurysm of the Abdominal Aorta, the Surgical, 879, of Nasopharyngeal Tumors, The Early Symptoms, 1058, Perianal Tuberculosis, 440, Prothrombin Deficiencies, Use of Intramuscular Injections of 2-Methyl-1, 4-Naphthoquinone in, 783, and Diagnosis of Gastric Lesions, 339
Tube, Intestinal, Fluid and Nutritional Maintenance by Use of an, 584
Tuberculosis, Perianal, Treatment of, 440, of the Stomach, 225, Pulmonary, Lobectomy and Pneumonectomy in, 201
Tumor, Metastatic Pulsating, of Bone Secondary to Renal Carcinoma, 249, of Pancoast, 1
Tumors, Benign, of the Bronchi, Thoracic Bronchotomy for Removal of, 1067, Nasopharyngeal, Early Symptoms and Treatment of, 1058, of Islet Cells with Hyperinsulinism, 161

TURELL, ROBERT Studies on Absorption of Sulfanilamide from Large Intestine, 417

U

Ulcer, Gastric, Subesophageal, Chronic Penetrating or Perforated, Electrosurgical Excision of, 219
Upper Extremity by Preganglionic Section, the Problem of Producing Complete and Lasting Sympathetic Denervation of, 1085
Ureteral Transplantation, 100

V

VALK, WILLIAM L Delayed Closure of Contaminated Wounds, 256
VAN DUYN, E S Suppurative Thrombophlebitis of Femoro-Iliac Vein with Blood Stream Invasion, 294
VAN DUYN, JOHN, 2nd Suppurative Thrombophlebitis of Femoro-Iliac Vein with Blood Stream Invasion, 294
VARCO, RICHARD L Gastric Acidity Before and After Operative Procedure with Reference to Role of the Pylorus and Antrum, 626
Varicose Veins, Circulatory Disturbances Produced by Extensive Angiomata of the Lower Extremities, Associated with, 960
Vascular Surgery, Personal Experiences in, 802
VERIOT, MAX G Neurogenic Disturbances of the Colon and Their Investigation by the Colonmetrogram, 1042
Vertebral Veins and Their Role in Spread of Metastases, Function of, 138
Vitamin K Activity in Treatment of Prothrombin Deficiencies, 783
Volvulus of Small Intestine, and Incomplete Rotation of, Ladd's Operation for Cure of, Producing Duodenal Obstruction in Infancy, 234
Vulvitis, Leukoplakic, 87

W

WALPOLE, STEWART Gastric Acidity Before and After Operative Procedure with Reference to Role of the Pylorus and Antrum, 626
WALTER, CARL W Relation of Proper Preparation of Solutions for Intravenous Therapy to Febrile Reactions, 603
WAITERS, WALTER Operative and Post-operative Infections with Reference to Air-Borne Bacterial Contamination, 271
WANG, SHOA-HSUN Metastatic Pulsating Tumor of Bone Secondary to Renal Carcinoma, 249

- WANGENSTEEN, OWEN H Gastric Acidity Before and After Operative Procedure with Reference to Role of the Pylorus and Antrum, 626
- WARREN, SHIELDS Carcinoma of the Thyroid, 977
- WHIPPLE, ALLEN O Address of President, 481
- WHITI, JAMES C Neurogenic Disturbances of the Colon and Their Investigation by the Colonmetrogram, 1042
- WHITE, WILLIAM C Irradiation Burn of the Intestine, 769
- WILLARD, DL FOREST Cyst of the Semilunar Cartilage, 305
- WISR, WALTER D Obituary of Alexis McGlannan, 798
- WOLFF, WILLIAM A Liver Damage and Dextrose Tolerance in Severe Burns, 158, Plasma Transfusion in Treatment of Fluid Shift in Severe Burns, 150
- Wound Infection, 280
- Wounds, Contaminated, Delayed Closure of, 256, Healing of, Critical Latent or Lag Period in, 481, Operative, Influence of Sutures upon, 112

Borrower's No. Due Date
 Borrower's No. Due Date
 A. C. B.

Journal Issue Card
 Journal Issue Card
 Journal Issue Card

JOURNAL

Of No.

Acc. No.

Title

Year

Vol.

Borrower's No. Due Date

Borrower's No. Due Date

Borrower's No. Due Date

Borrower's No. Due Date